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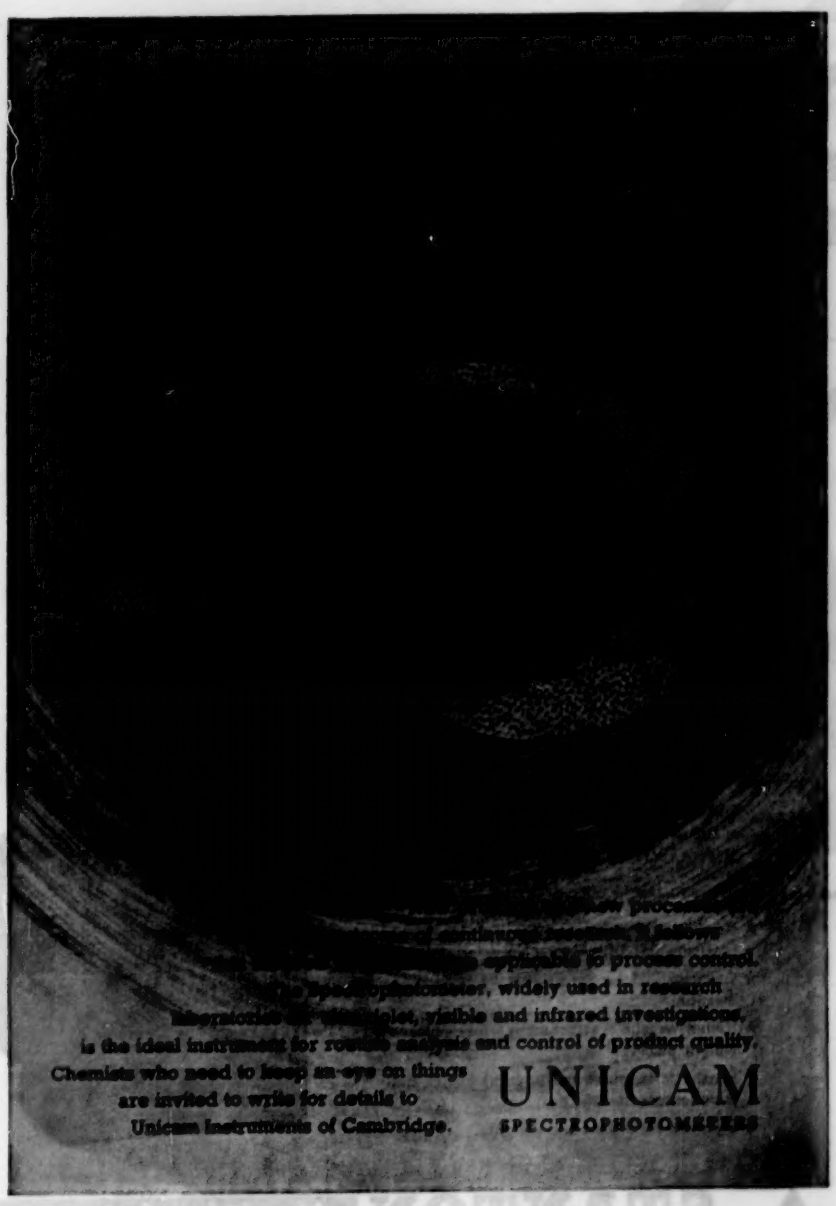
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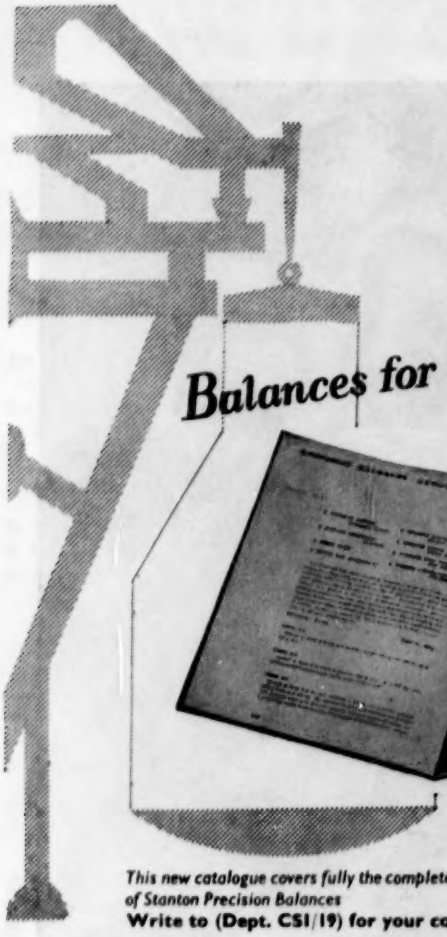

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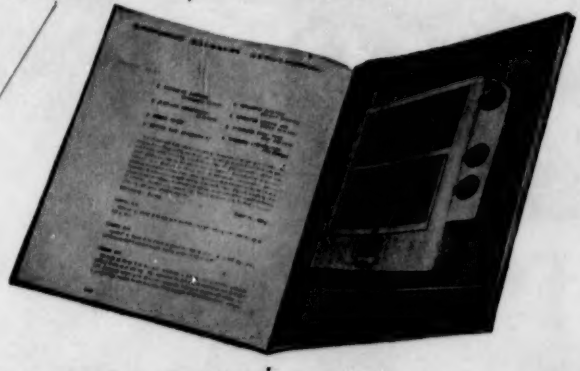

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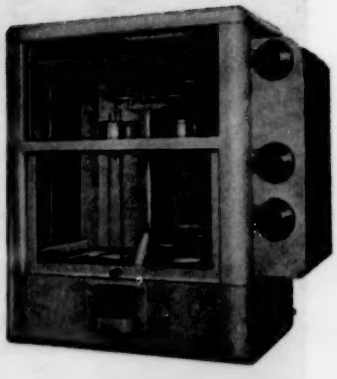

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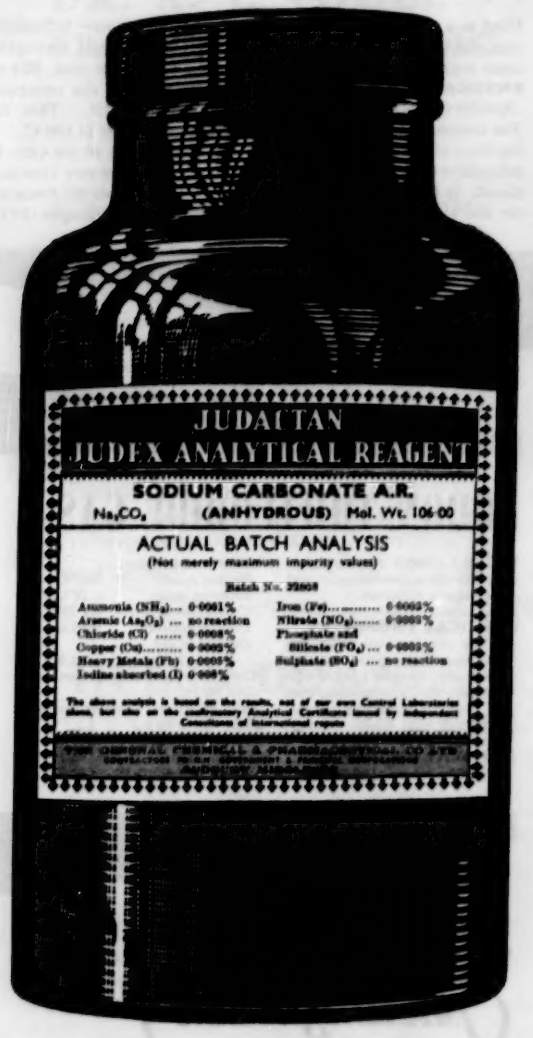
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48. *The Infrared Spectra of Liquid and Solid Formic Acid.*

By D. Chapman.

The infrared spectra of liquid and solid formic acid have been obtained between 3500 and 650 cm.$^{-1}$. The former spectrum shows that formic acid does not exist in dimeric units except on dilution with a solvent. The bands in the latter have been assigned to their corresponding molecular vibrations. The spectrum for the solid is reasonably consistent with the information from *X*-ray analysis that it exists as polymer, but not consistent with the measured C–O and C=O bond lengths.

The infrared spectra of formic acid as vapour and in solution have received particular attention.[1] No study of the acid in either the liquid or the solid state has been published, though Randall, Fowler, Fuson, and Dangl [2] have recorded (without comment) the spectrum of the liquid between 3500 and 650 cm.$^{-1}$.

The spectra for these states are of importance since there is evidence to suggest that this acid, unlike most other carboxylic acids, is not dimeric in the liquid or the solid state but is associated as a polymer. Dielectric-polarisation measurements [3] of the acid in the liquid and the solid state indicate that there must be a significant contribution from polar configurations rather than from non-polar dimers; this is in contrast with results for liquid acetic acid where the dielectric values confirm the dimeric condition.

The recent *X*-ray analysis [4] of solid formic acid shows that the molecules of formic acid in this state are linked by hydrogen bonds at both ends, forming infinite chains and not dimeric units. It suggests a considerable decrease (about 0·1 Å) in the C–O bond length in the transition from formic acid vapour to the solid (cf. Davies and Thomas [5]).

Materials and Apparatus.—Anhydrous formic acid was obtained by treating 98% commercial formic acid with a small excess of phosphoric oxide and cooling the mixture. This product was distilled under reduced pressure, and a middle fraction taken.

The liquid-state spectrum was obtained in the usual manner, with rock-salt flats. The solid-state spectrum was obtained by means of a transmission-type, evacuated, low-temperature cell, with liquid oxygen as a refrigerant.

The spectrometer was a Grubb-Parsons double-beam spectrometer with a rock-salt prism. The spectra were obtained between 3500 and 650 cm.$^{-1}$. Duplicate spectra of the liquid were obtained and the spectrum of the solid was obtained a number of times.

Results and Discussion.—Liquid formic acid. This gave bands at *ca.* 3151(s), *ca.* 2999(s), 2768(m), 2571(m), 2361(w), *ca.* 1724(s), 1391(sh), 1362(s), 1195(s), 1067(w), 1019(w), 875(w), and 669(w) cm.$^{-1}$.

The infrared spectra of a considerable number of carboxylic acids and their deuterated derivatives have been investigated between 1500 and 500 cm.$^{-1}$, as dimeric units in the liquid or crystalline solid state.[6] Under these conditions the carboxyl group gives rise to absorption bands in the regions 1420 $\pm$ 20, 1300 $\pm$ 15, and 935 $\pm$ 15 cm.$^{-1}$. The first two of these correspond to closely coupled OH deformation vibrations occurring in the plane of the ring formed by two carboxyl groups, whilst the last is caused by the out-of-plane OH deformation vibration.

In liquid formic acid strong absorption bands occur at 1391 (sh), 1362, and 1195 cm.$^{-1}$ (see Fig. *a*). There are no strong bands in the range 1300 $\pm$ 15 or 935 $\pm$ 15 cm.$^{-1}$. Only

[1] (*a*) Bonner and Hofstadter, *J. Chem. Phys.*, 1938, **6**, 531; Van Zandt Williams, *ibid.*, 1947, **15**, 232, 243; Herman and V. Williams, *ibid.*, 1940, **8**, 447; (*b*) Orville Thomas, *Discuss. Faraday Soc.*, 1950, **9**, 339; (*c*) Sverdlov, *Dokłady Akad. Nauk S.S.S.R.*, 1953, **91**, 503.

[2] Randall, Fowler, Fuson, and Dangl, "Infra-red Determination of Organic Structures," Van Nostrand, New York, 1949, p. 103.

[3] Johnson and Cole, *J. Amer. Chem. Soc.*, 1951, **73**, 4536.

[4] Holtzberg, Post, and Fankuchen, *Acta Cryst.*, 1953, **6**, 127.

[5] Davies and Orville Thomas, *Research*, 1951, **4**, 384.

[6] Hadzi and Sheppard, *Proc. Roy. Soc.*, 1953, *A*, **216**, 247.

a weak absorption centred about 875 cm.$^{-1}$, spreading from 994 to 745 cm.$^{-1}$, occurs, instead of the usual intense out-of-plane OH deformation band found in all dimeric acids.

This evidence suggests that liquid formic acid is not dimeric. Examination of formic acid in solution in carbon tetrachloride confirms this interpretation. The spectra of the liquid, and of concentrated solutions of formic acid, are quite different. A strong band at 927 cm.$^{-1}$ occurs at high concentrations (but vanishes on dilution as the amount of monomer increases), and has been assigned to a dimeric vibration.[1b] Further, with concentrated solutions, there is no band at 1195 cm.$^{-1}$ but on dilution a band appears at 1208 cm.$^{-1}$ which has been assigned to a monomer vibration.[1b]

Thus the infrared evidence shows that formic acid is neither monomeric nor dimeric in the liquid state. On dilution in carbon tetrachloride, the polymer presumably splits to form dimeric units which on further dilution split to give monomers.

It is of interest to consider the frequencies of the absorption bands in the associated OH region of the liquid acid. Davies and Evans[7] have pointed out that the structure of the associated bands in solutions of certain amides and of trichloroacetic acid can

FIG. *a*.

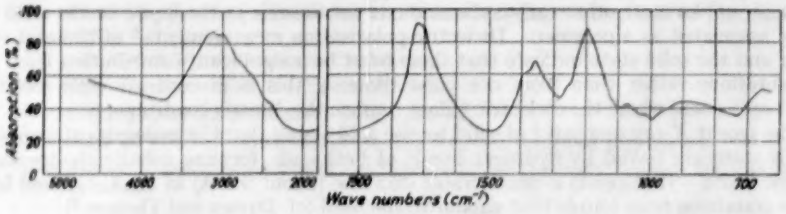
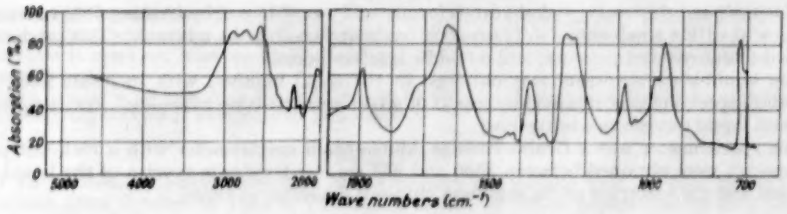


FIG. *b*.



apparently be accounted for in terms of sums and differences between the OH (or NH) stretching frequency and low frequencies of the order of 70—200 cm.$^{-1}$. The latter are attributed to the associated molecule.

The bands due to association are at 3151, 2768, 2571, and 2361 cm.$^{-1}$. By starting from the 3151 cm.$^{-1}$ feature the others occur at intervals of 383, 580, and 790, which may be expressed revealingly as *ca.* 2 × 190, 3 × 193, and 4 × 195. The hydrogen-bridge frequency (ν_1 of the linear X–H—Y) directly observed in formic acid liquid has been observed in the Raman spectrum[8] at ~180 cm.$^{-1}$. Thus it seems plausible to identify the bands in the "associated OH" region as overtones of this frequency. It should be noted, however, that the extra peaks in the 3μ region in formic acid vapour, and in liquid acetic acid, have been interpreted in terms of summation bands due to appropriate combinations of fundamental vibrations of the coupled carboxyl groups of the dimeric molecules[9]. Davies and Evans[7] suggest that the combination tones may be more clearly resolved the more definite the structure of the associated species, and compare the carboxyl dimer (as in trichloroacetic acid) with the chain-associating alcohols. With liquid formic acid it appears that even in the polymeric form the associated OH region can be clearly resolved.

[7] Davies and Evans, *J. Chem. Phys.*, 1952, **20**, 342.
[8] Hibben, "The Raman Effect and its Chemical Applications," Reinhold Publ. Corp., New York, 1939, p. 180.
[9] Bratož, Hadži, and Sheppard, *Bull. sci. Conseil Acad. R.P.F., Yougoslavie*, 1953, **1**, 71.

Solid formic acid. A theory of the infrared spectra of crystals at low temperatures has been given by Winston and Halford,[10] and by Hornig.[11] Hornig points out from a comparison of experimental results that there is, in general, a correlation between a frequency of the free molecule in the gas and a set of crystalline frequencies, but that both shifts of frequency and coupling effects must be taken into account. Further, he shows that the spectrum for the crystalline state is determined by the site symmetry of the molecules in the unit cell and by the symmetry of the unit cell.

It seems reasonable, as a first approximation, to discuss the spectrum of solid formic acid by analogy with the frequencies of the monomeric vapour (as determined and assigned by Orville Thomas [personal communication (see Table)]. Whilst there is a molecular plane of symmetry in the formic acid molecule in the vapour state, this is not the case for the polymerised molecule in the solid state. Furthermore, allowance must be made for the influence of the V_J' perturbation, *i.e.*, the change in V_J^0 the potential energy function of the free molecule due to the equilibrium field of the crystal, and of the V_{JK}'' perturbation (the interaction between the displacement co-ordinates of the jth and the kth molecule). Shifts in frequency due to the perturbation V_J' will not be too great, perhaps about 20 or 30 cm.$^{-1}$ (cf. benzene), whilst larger shifts (100 cm.$^{-1}$) such as are reported [11] to occur in hydrogen-bonded substances are almost certainly due to changes in the lengths of the bonds involved in the hydrogen bonding. The V_{JK}'' perturbation is the coupling term and will produce splitting of the frequencies corresponding to each non-degenerate vibration of the free molecule. The number of such components observed in the infrared spectrum of the crystalline solid depends on the number of molecules per unit cell and the symmetry of the point group.

The X-ray measurements [5] of the formic acid crystal show that there are four molecules per unit cell, and the space group of the unit cell is Pna(C_{2v}^9). The point group is, therefore, C_{2v} and the site symmetry is C_1. From this it can be deduced that all fundamental vibrations of the molecule will be infrared-active. The number of components for each vibration will be four, of which three will be active in the infrared (A_1, B_1, and B_2) and all of which will be active in the Raman effect (A_1, A_2, B_1, B_2).

The spectrum of the solid differs considerably from that of liquid formic acid, with an increase in the number of absorption bands (Fig. *b*). A closer analogy is usually observed between the spectra of the liquid and the crystalline phase of non-polar molecules. With polar molecules, however, particularly where hydrogen bonding occurs, marked modifications can occur in the spectrum. The frequencies for the solid state are given in the Table.

Three strong bands occur, at 2921, 2744, and 2562 cm.$^{-1}$, which can be assigned to the set of three frequencies associated with the OH stretching vibration, in agreement with the predicted splitting expected for the point and site symmetry deduced from the X-ray evidence. The shift in frequency from the monomer frequency in the vapour (3569 cm.$^{-1}$) to the mean position of the three components in the spectrum of the solid is 825 cm.$^{-1}$. Such a considerable shift in this frequency is fairly consistent with the X-ray measurements. The O–H–O distance in the polymer is estimated to be 2·58 Å. This distance in the dimer is 2·73 Å, and the OH stretching frequency of the dimer is at 3080 cm.$^{-1}$, $\Delta\nu$ in this case being 489 cm.$^{-1}$.

It is to be expected that the C–H stretching frequency for the solid will not be altered greatly from that observed for the vapour (2943 cm.$^{-1}$) since this bond is not intimately connected with association. Owing to overlapping of the OH absorption in the spectrum, however, it is not possible to observe clearly the C–H stretching frequency. There is an inflexion on the side of the 2921 cm.$^{-1}$ band which may be due to this vibration.

There are a number of unusual weaker bands occurring between the OH and the C=O regions of the spectrum for the solid. Thus, there are bands at 2464, 2387, 2312, 2143, 2074, 1922, and 1894 cm.$^{-1}$. The origin of these bands is obscure. By starting from the 2464 cm.$^{-1}$ feature the others occur at intervals of 77, 152, 321, 390, 541, 551, and 570 cm.$^{-1}$.

[10] Winston and Halford, *J. Chem. Phys.*, 1949, **17**, 607.
[11] Hornig, *ibid.*, 1948, **16**, 1063; *Discuss. Faraday Soc.*, 1950, **9**, 115.

These do not seem to fit into any marked sequence analogous to that obtained for the " associated OH " band in the spectrum of the liquid and may be combinations of fundamental vibrations and lattice vibrations.

Gas monomer frequencies (cm.$^{-1}$)	Mode of vibration of free molecule : description	symmetry	Crystal (cm.$^{-1}$)	Frequency shift, gas to solid (cm.$^{-1}$)	Splitting (cm.$^{-1}$)
3569	OH	A′	2921 s 2744 s 2562 s	825	177 182
2943	CH	A′	Inflexion on side of 2921 cm.$^{-1}$ band (?)		
	Combination bands (?)		2464 (sh) 2387 (sh) 2312 w 2143 m 2074 w 1922 w 1894 m		
1773	C=O	A′	1723 m 1638 s (sh)	− 93	85
1107	C–O	A′	1265 s 1240 s 1218 s	+133	25 22
658	δ(OCO)	A′	725 s 715	+ 60	10
1380 1232	δ(CH) δ(OH)	A′ (in plane)	1447 w 1426 w 1374 m 1333 w	− 6	
	δ(OH)	A″ (out of plane)	988 s 959 s		29
1033	δ(CH)	A″ (out of plane)	1080 s	+ 47	

The electron diffraction and *X*-ray measurements indicate that the C=O distance is the same (within the limits of error) in the vapour and the solid state. This seems somewhat surprising in view of the considerable decrease observed in the C–O bond length in the transition from vapour to solid. If this is the case, however, then the mean frequency of the components of the carbonyl vibration would be expected to be near the frequency of the analogous vibration in the monomer spectrum. The monomer frequency is at 1773 cm.$^{-1}$. The frequencies for the solid state most reasonably assigned to carbonyl vibration are at 1638 and *ca.* 1723 cm.$^{-1}$. The mean frequency of these components is at 1680 cm.$^{-1}$, a quite considerable shift ($\Delta\nu = 93$ cm.$^{-1}$) from the monomer frequency. The infrared evidence, therefore, indicates that the C=O bond length is not the same in both the solid and the vapour state.

Electron-diffraction and *X*-ray measurements indicate that the C–O bond length decreases by at least 0·1 (±0·03) Å during the transition from formic acid vapour to solid. Calculations by Davies and Sutherland [12] indicate that a transition of this type might result in a decrease in the bond length of the order of 0·04 Å. Holtzberg *et al.*[4] suggest that, if the electron-diffraction and *X*-ray measurements are both correct, then the differences in bond length cannot be attributed entirely to the vapour–solid transition. A very recent determination of the bond length in the vapour state by an electron-diffraction method [13] confirmed the earlier value for the monomer. It is of interest, therefore, to see whether the spectrum of the solid is consistent with a marked decrease of the C–O bond length.

The frequency assigned to the C–O vibration in the spectrum of the monomer is at 1107 cm.$^{-1}$. The most reasonable assignment of this vibration in the spectrum of the solid is to the set of three frequencies at 1265, 1240, and 1218 cm.$^{-1}$. The bond will certainly acquire more double-bond character in the solid state and hence it is unlikely to give rise to the band at 1080 cm.$^{-1}$. Of the bands at *ca.* 1374 cm.$^{-1}$ and those at *ca.* 1240 cm.$^{-1}$ the latter are preferred in view of their greater intensity, since the increase of double-bond character and the fact that the vibration is a stretching mode will be expected to give rise to a set

[12] Davies and Sutherland, *J. Chem. Phys.*, 1938, **6**, 755.
[13] Karle and Karle, *ibid.*, 1954, **22**, 43.

of component bands of high intensity. (A study of the deuterated material could confirm this assignment.)

On this assignment the shift in frequency ($\Delta\nu$) from the C–O frequency in the monomer to the mean component in the solid is +133 cm.$^{-1}$. The shift from the C=O frequency in the monomer to the corresponding mean component in the solid is −93 cm.$^{-1}$. It is not inconsistent that a corresponding increase in the C–O bond frequency should tend to accompany a decrease in the C=O bond frequency.

It is possible by means of Clark's relation [14] to estimate approximately the decrease in bond length of the C–O bond in the solid state from that observed in the vapour state, by using the increase in the C–O frequency in the spectrum of the solid over that obtained for the vapour. This leads to a decrease in value (1240 cm.$^{-1}$ being used as the C–O frequency) of ~0·05 Å in the bond length. This is in fairly good agreement with Davies and Sutherland's calculations.[12]

Note added in Proof.—W. J. Orville Thomas has recently re-examined his assignments of the frequencies in the monomer, and now suggests that coupling occurs between the ν(C–O) and δ(OH) in-plane vibrations. He suggests that the uncoupled ν(C–O) in the monomer may be at ~1180 cm.$^{-1}$. In solid formic acid, owing to the decrease in the C–O bond length, decoupling of these vibrations may be expected. On this new basis $\Delta\nu$ for the ν(C–O) frequencies for the vapour to solid transition is ~60 cm.$^{-1}$, and the change in the C–O bond length from vapour to solid is even less than that predicted in the present paper. The less plausible assignment of the band at *ca.* 1374 cm.$^{-1}$ in the solid state spectrum to the ν(C–O) mode, would give a shift more consistent with the *X*-ray evidence.

In the vapour state the δ(OH) A′ frequency occurs at 1232 cm.$^{-1}$. In dimeric formic acid in solution a shift to 1364 cm.$^{-1}$ is observed. This 1364 cm.$^{-1}$ band completely masks the δ(CH) A′ vibration which occurs in the same region. The δ(CH) A′ frequency in the spectrum of the solid will not be altered appreciably from that observed for the vapour since it is not intimately concerned with hydrogen bonding. It seems reasonable to suppose, therefore, that the set of frequencies at *ca.* 1374 cm.$^{-1}$ for the solid could correspond to a superposition of the shifted δ(OH) A′ frequency of the vapour on the δ(CH) frequency.

The δ(OH) A″ frequency has not been observed in the vapour (monomer), but in the dimer is at 927 cm.$^{-1}$. A corresponding shift to the set of frequencies at *ca.* 974 cm.$^{-1}$ seems a reasonable assignment for a δ(OH) vibration in the spectrum of the solid.

In the crystalline state the acids existing in dimeric form (*e.g.*, lauric acid) give an intense broad band associated with the out-of-plane OH deformation vibration at 935 ±15 cm.$^{-1}$. The bands at *ca.* 974 cm.$^{-1}$ in solid formic acid assigned to a δ(OH) vibration are outside this range, and are neither as broad nor as intense.

The δ(CH) A″ frequency for the vapour (monomer) occurs at 1033 cm.$^{-1}$, in solution in carbon tetrachloride at 1064 cm.$^{-1}$, and at 1069 cm.$^{-1}$ in the formate ion. The band at 1080 cm.$^{-1}$ for the solid is, therefore, assigned to a C–H deformation vibration.

Finally the set of frequencies at *ca.* 710 cm.$^{-1}$ in the spectrum of the solid is assigned to the δ(OCO) vibration by analogy with the assignment of this vibration in the monomer to the frequency 658 cm.$^{-1}$.

These conclusions are summarised in the Table, the mean of the component frequencies being used to compute the frequency shift. Both the shift and the splitting effects are greater for the OH stretching vibrations than for any other vibration.

The author thanks Dr. J. H. Rayner for an interesting discussion of the *X*-ray structure of formic acid.

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[*Received, June 9th, 1955.*]

[14] Clark, *Phil. Mag.*, 1934, **18**, 459.

49. *The Diffusion Coefficient of Hydrogen in Iron.*

By T. M. Stross and F. C. Tompkins.

The diffusion coefficient D of hydrogen in iron has been evaluated in the temperature range 150—900° from measurements on the rate of evolution into a vacuum from an iron cylinder saturated with hydrogen under various conditions. Values of D are given by the equation

$$D = (5{\cdot}31 \pm 0{\cdot}50) \times 10^{-3} \exp[(-3050 \pm 100 \text{ cal.})/RT] \text{ cm.}^2 \text{ min.}^{-1}$$

These are compared with previous results obtained by the permeation method. The present work indicates that rate-determining processes are absent at the exit surfaces of the iron, and are probably so at both exit and entry surfaces in permeation studies.

Various methods [1-14] have been used to obtain the diffusion coefficient of hydrogen in iron but only those involving the measurement of steady-state permeability rate,[11-14] and the related time-lag [10] in attaining the steady state, appear to give consistent results. In the former methods, the diffusion coefficient D is evaluated from the flux J for the diffusion of the gas through unit area of membrane from the equation

$$J = -D\mathrm{d}C/\mathrm{d}x \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $\mathrm{d}C/\mathrm{d}x$ is the concentration gradient of the diffusing species within the metal.

The activation energies for permeation through (E_P) and diffusion within (E_D) the metal are defined by the equations

$$P = P_0 \exp(-E_P/RT) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$D = D_0 \exp(-E_D/RT) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where P is the permeability constant, or the rate of permeation under standard conditions. Since this rate is proportional to the concentration gradient of dissolved hydrogen in the metal, E_D can be calculated from E_P and the temperature coefficient of the solubility of the gas in iron, provided that phase-boundary reactions at the iron surfaces do not control the rate.

We measured the rate of evolution of gas from a solid, iron cylinder at constant temperature into a vacuum. This method has the disadvantage that the measured rate might be sensitive to phase-boundary processes at the exit surface, but the experimental evidence points to their absence. The advantages of the method are that (i) it eliminates surface processes at the entry face in permeability measurements that might be rate-determining; (ii) the exit surfaces of the cylinder can be kept very clean; alternatively they can be deliberately contaminated by sorption of other gases in order to test whether the evolution rate is affected by surface conditions; (iii) the solution of Fick's law for diffusion of gas (with constant D) out of a finite cylinder is available.[3]

Experimental

Materials.—Vacuum-cast rods of iron were supplied by the British Iron and Steel Research Association and contained C, 0·002; Si, 0·004; Mn, 0·005; S, 0·004; P, 0·001; Ni, 0·012; Cu,

[1] Tamman and Schneider, *Z. anorg. Chem.*, 1928, **172**, 43; [2] Moore and Smith, *Trans. Amer. Inst. Mech. Eng.*, 1939, **135**, 255; [3] Andrew, Mallik, and Quarrel, *J. Iron Steel Inst.*, 1946, **153**, 67; [4] Demarez, Hock, and Meuner, *Acta Met.*, 1954, **2**, 214; [5] Fast, *Phillips Tech. Rev.*, 1942, **7**, 74; [6] Betz, *Z. Physik*, 1940, **117**, 100; [7] Ham and Rast, *Trans. Amer. Soc. Metals*, 1938, **25**, 886; [8] Ham, *ibid.*, 1937, **25**, 526; [9] Bhat and Lloyd, *J. Iron Steel Inst.*, 1950, **165**, 382.

[10] Barrer, *Trans. Faraday Soc.*, 1940, **36**, 1235.

[11] Smithells and Ransley, *Proc. Roy. Soc.*, 1935, *A*, **150**, 172.

[12] Borelius and Lindblom, *Ann. Physik*, 1927, **82**, 201.

[13] Ryder, *Electronics*, 1920, **17**, 161.

[14] Post and Ham, *J. Chem. Phys.*, 1937, **5**, 913.

0·005; Al, 0·003; O, 0·0016; N, 0·0014%. Small cylinders (~3 cm. in length, 1·13 cm. in diam.) were machined from the rods but not polished. Hydrogen from a cylinder was purified by passage through a 30-cm. column of palladised asbestos at 300°, phosphoric oxide, and finally activated outgassed charcoal cooled in liquid nitrogen.

Apparatus.—This comprised a conventional high-vacuum system with a two-stage mercury diffusion pump, calibrated McLeod and Pirani guages, and a furnace section. Traps cooled in liquid nitrogen prevented access of mercury vapour to the iron from mercury cut-offs, etc. A transparent silica tube, 75 mm. long and of 16 mm. int. diam., formed the core of the furnace which was controlled manually within about ±1°. Through one end of the tube was sealed a Pt/Pt–Rh thermocouple in an open silica sheath to allow the junction to be placed in direct contact with the iron cylinder. The latter was contained in a tungsten-wire cradle which was attached by silica fibres to silica-enclosed iron slugs so that the specimen could be moved in and out of the furnace by means of a magnet.

Procedure.—Before use, the iron was outgassed at 1000°, exposed to 1 atm. of hydrogen for 2 hr. at 900°, and further outgassed for 16 hr. at 1000°. For any run, the iron was saturated with hydrogen under standard conditions, *viz.*, unless otherwise stated : 1 atm. hydrogen for 16 hr. at 800° (*i.e.*, below the α—γ transition temperature), although as judged from the reproducibility of results, 2 hr. appeared to be adequate for saturation. After saturation the specimen was transferred by means of the magnet to a section of the apparatus that was cooled to −78° in a solid carbon dioxide–acetone bath; after 20 min. the hydrogen in the gas phase was evacuated.

As hydrogen is appreciably soluble in silica at high temperatures, the tube was heated to 1000° and evacuated for 2 hr. after the iron had been removed from the furnace. The temperature was then lowered to that required for the subsequent measurement of the rate of evolution, and the residual rate of outgassing into vacuum measured. The iron cylinder was then transferred from the cold trap to the furnace. Independent experiments with the thermocouple junction placed inside a cavity in the centre of the specimen showed that temperature equilibrium with the furnace was established within 6 min.

The rate of evolution was determined by a differential method, *i.e.*, by recording at convenient times the time interval Δt required for a definite pressure increase Δp at a mean pressure of $2{\cdot}5 \times 10^{-4}$ mm. Between measurements the evolved hydrogen was evacuated. Finally, the iron was removed and the outgassing rate from the silica tube again recorded. The results presented have been corrected for this additional rate of evolution from the silica tube.

Calculation of Results.—The solution of Fick's equation [3] for the rate of gas evolution applied to a cylinder of radius r (cm.) and length l (cm.) having an initial uniform concentration c of gas (in arbitrary units) is

$$-\frac{\mathrm{d}Q}{\mathrm{d}t} = 32\frac{Q_0K}{\pi^2\beta^2}\exp\left(-KDt\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

if it is assumed (i) that $c = 0$ at $r = r_0$ for $t > 0$ (since the gas is evolved into a vacuum), and (ii) that D is independent of the concentration of hydrogen within the metal.

Q_0 is the initial quantity of gas in the specimen, and K is a constant determined from its dimensions.[3] For a cylinder

$$K = \pi^2/l^2 + \beta^2/r_0^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where β is the first root of the Bessel function of the first kind and zero order.

Since the gas was evolved into a constant volume and the increase of resistance (ΔR) of the Pirani guage was linearly related to the pressure increase Δp, then, from equation (4), the plot of $\log_{10}(\Delta R/\Delta t)$ against t (in min.) should be a straight line of gradient $-0{\cdot}434KD$; from this, D can be evaluated in units of cm.^{2} min.$^{-1}$.

Results and Discussion

Some typical plots of $\log_{10}(\Delta R/\Delta t)$ against t for various temperatures are given in Fig. 1; they show that equation (4) is valid after an initial period which, except at the highest temperatures, is longer than that required for the establishment of thermal equilibrium (~6 min.). The reproducibility of results for the gradient of the plots ($-0{\cdot}434KD$) was usually about 4% although in some runs (cf. Fig. 2) the scatter of results was larger.

Fig. 2 shows the plot of log D against $1/T°$ (K) for one specimen from which, by the least-squares method, we obtain

$$D = 6{\cdot}9 \times 10^{-2} \exp(-3220 \text{ cal.}/RT) \text{ cm.}^2 \text{ min.}^{-1} \quad . \quad . \quad . \quad . \quad (6)$$

From all the results obtained with six different specimens,

$$D = (5{\cdot}31 \pm 0{\cdot}50) \times 10^{-2} \exp[(-3050 \pm 100) \text{ cal.}/RT] \text{ cm.}^2 \text{ min.}^{-1} \quad . \quad . \quad (7)$$

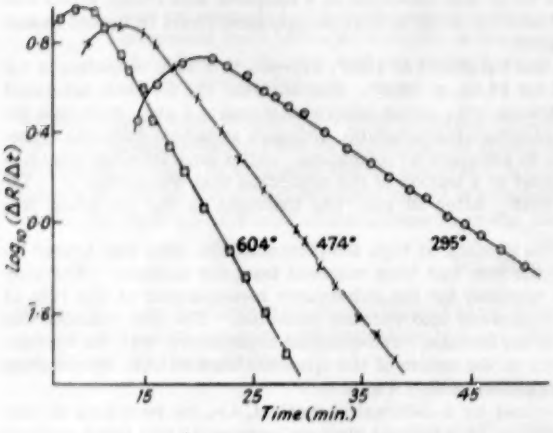

FIG. 1. *Plot of log* $(\Delta R/\Delta t)$ *against* t. *The gradient of the linear section equals* $-0{\cdot}434KD$, *where* K *is a constant and* D *the diffusion coefficient.*

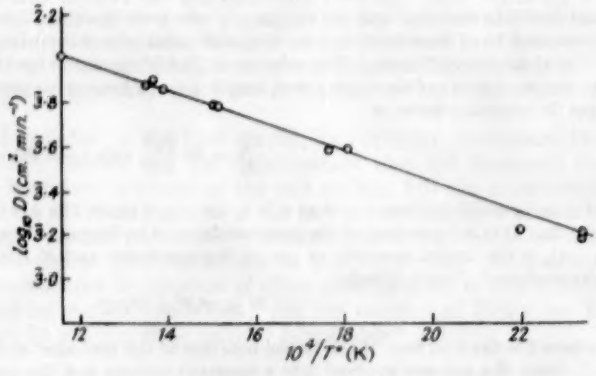

FIG. 2. *Plot of* $\log_{10} D$ *against* $1/T°$ (K) *for one specimen.* $E = 3220$ *cal./mole*$^{-1}$.

where E_D is expressed in cal. mole^{-1}. It must be emphasised that equation (4) is only valid if D is a constant independent of the concentration of hydrogen within the metal, and rate-determining processes at the exit surface of the metal are absent.

Constancy of D.—The concentration of hydrogen dissolved in the iron was varied ninefold by saturating at 800° under various hydrogen pressures. The gradients, however, were constant within the experimental uncertainty (4%), although, of course, the heights of the maximum of the plot were different. Similarly, during any run, despite large changes in the hydrogen content of the iron, the gradient remained constant. This conclusion might have been expected because of the low solubility of hydrogen in iron so that the solution is always very dilute. Neither the temperature nor the duration of saturation of the iron with hydrogen affected the value of D at a particular temperature.

Phase-boundary Processes.—Their absence at the exit surface was confirmed by the following experiments.

(i) From the heats of adsorption of hydrogen on iron and their variation with coverage [15] we calculate that at a pressure of $1{\cdot}5 \times 10^{-2}$ mm. at 150°, about 25% of the iron surface should be covered with adsorbed gas, whereas at $2{\cdot}5 \times 10^{-4}$ mm. and 150° the coverage is less than 5%. Nevertheless, the rates of evolution into atmospheres of hydrogen at these two (constant) pressures were the same within experimental error.

(ii) Similarly, the surface was contaminated with nitrogen by using 3 cm. pressure of the gas at various temperatures from 20° to 450° after the specimen had been saturated with hydrogen. Even at the highest temperature, because of the high heat of chemisorption,[16] 10% of the surface should be covered. Even so, no difference in the rates compared with that from an uncontaminated surface was found. Treatment with ammonia at 450°, thereby forming surface nitrides [17] from which the evolution of nitrogen is slow because of the high activation energy (42 kcal. mole^{-1}), was also ineffective.

(iii) Oxygen is strongly chemisorbed [16] and surface oxidation takes place below 0°; these surface oxides are, moreover, not completely removed by reduction with hydrogen at 500°. Despite this, treatment of the iron after saturation with hydrogen with 1 cm. pressure of oxygen at temperatures between 23° and 500° had no effect, nor did preliminary repeated oxidations and reductions of the surface layers.

It is therefore concluded that the rate of diffusion within the metal was the rate-determining process and the measured rate was not associated with any phase-boundary phenomena.

The Maximum Rate of Evolution.—Application of Fick's law with a constant value of D shows that the maximum rate should be attained as soon as the sample has acquired the furnace temperature, *i.e.*, within six minutes or less after transference of the specimen from the cold trap to the furnace. Actually the rate increased to a maximum after much longer periods, the time interval being greater the lower the temperature of the evolution measurements. This initial lower rate is due to the fact that when the sample was cooled from 800°, the temperature of saturation, to −78°, hydrogen was evolved from the outer layers because its solubility is less at lower temperatures, and the rate of cooling was not sufficiently rapid to "freeze" the solubility equilibrium established at 800°. Consequently, at the commencement of the rate measurements the concentration of hydrogen in the outer layers was smaller than that in the bulk; since the cooling conditions were standardised, this lower concentration was in each case the same at the beginning of each rate measurement. It follows that the time lag before the attainment of a uniform concentration throughout the specimen, or the time, $t_{max.}$, which elapsed before the maximum rate of evolution was reached, is inversely proportional to the value of the diffusion coefficient at the temperature of the rate measurements. Consequently, as found experimentally, the plot of log $(1/t_{max.})$ against $1/T°$ (K), though showing some scatter, is linear and from the slope of the line we calculate the temperature coefficient of D to be associated with an activation energy of 2·7 kcal. mole^{-1}, in fair agreement with the value of $3{\cdot}0 \pm 0{\cdot}1$ kcal. mole^{-1} obtained from the gradient $-0{\cdot}434KD$ of the later, main evolution process. Better agreement is not expected since the value of $t_{max.}$ includes the variable time taken for the specimen to attain the different temperatures of the rate measurements. Some confirmation of this explanation of the position of the maxima is afforded by the increase of $t_{max.}$ and the decrease of height of the maximum when the rate of cooling was decreased, although the gradients of the later linear section of the plot were the same.

Comparison with Previous Results.—Values of D at various temperatures for the hydrogen–iron system have been obtained by applying the time-lag method [10] to the early results of Edwards [18] on the rate of permeation of nascent hydrogen through iron. These are [cf. eqn. (7)] given by:

$$D = 1{\cdot}63 \times 10^{-2} \exp(-9200/RT) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

[15] Bagg and Tompkins, *Trans. Faraday Soc.*, 1955, **51**, 1071.
[16] Beeck, *Adv. Catalysis*, 1950, **2**, 151.
[17] Goodeve and Jack, *Discuss. Faraday Soc.*, 1948, **4**, 52.
[18] Edwards, *J. Iron Steel Inst.*, 1924, **60**, 9.

Later measurements,[10] using activated iron, gave a lower activation energy of 6·74 kcal. Andrew *et al.*,[3] using the evolution method over the temperature range 550—1100°, report E_D to be 5·75 kcal. for austenitic steels but this higher value than ours for α-iron might be expected. Demarez, Hock, and Meunier[4] have recently recorded values between $0{\cdot}93 \times 10^{-4}$ and $2{\cdot}67 \times 10^{-4}$ cm.^{2} sec.$^{-1}$ at 650° for mild steels from rates of evolution and these are in good agreement with the value of $1{\cdot}70 \times 10^{-4}$ cm.^{2} sec. calculated from equation (7) at this temperature.

There is good agreement among the results of Smithells and Ransley,[11] Borelius and Lindblom,[12] Ryder,[13] and Post and Ham[14] (below 900°) on the rates of permeation of hydrogen through iron. If the permeability constant P is defined as the steady-state rate in cm.^{3} (S.T.P.) per min. per cm.^{2} surface through 1 cm. of iron for hydrogen on the entry side at 1 atm. into a vacuum on the exit face, their results have a mean value of

$$P = 11{\cdot}3 \times 10^{-3} \exp(-9600/RT),$$

where the activation energy is in cal. mole^{-1}.

Now, provided phase-boundary processes are absent, $P = -D\mathrm{d}C/\mathrm{d}x$. Consequently, if the solubility S is expressed in units of cm.^{3} of hydrogen (S.T.P.) per cm.^{3} of iron at 1 atm.

$$P = D_0 S_0 \exp[-(E_D - Q)/RT] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

where $S = S_0 \exp(-6700/RT)$, $S_0 = 0{\cdot}156$,[15] and Q, the heat of solution,[16] is in cal. mole^{-1}. Hence we calculate from equation (9) that $E_D = 2900$ cal. mole^{-1} and $D_0 = 8 \times 10^{-3}$ cm.^{2} min.$^{-1}$ in good agreement with our values of 3050 cal. mole^{-1} and $5{\cdot}3 \times 10^{-3}$ cm.^{2} min.$^{-1}$ respectively.

There is some confusion, or inconsistency, in the literature concerning the units of the energy terms, E_P, E_D, and Q (cf. Smithells and Ransley[11]); we have therefore consistently expressed these energies in terms of the measured quantity, *viz.*, moles of hydrogen evolved into, or taken up from, the gas phase. No assumption is therefore made about the nature of the dissolved species or of that responsible for the passage of gas through or out of the metal.

The fact that the results of permeability measurements agree well with those obtained from our values of the rates of evolution (where surface processes are proved not to be rate-determining) suggests that phase-boundary prosesses are likewise unimportant from the kinetic viewpoint at both exit and entry surfaces in permeation measurements. Although surface treatment affects rates of permeation, the differences are small. With iron at 863° K the ratios of the permeability constants for a polished surface and for one that has been oxidised and reduced at 800° are only 1 : 1·2; and even after etching the rate is increased only ten-fold.[11] Such comparatively small differences are probably associated with changes in the actual external surface readily accessible to the gas as distinct from the geometric area, and not due to contaminants in the surface layers.

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S. Kensington, London, S.W.7. [*Received, June 23rd,* 1955.]

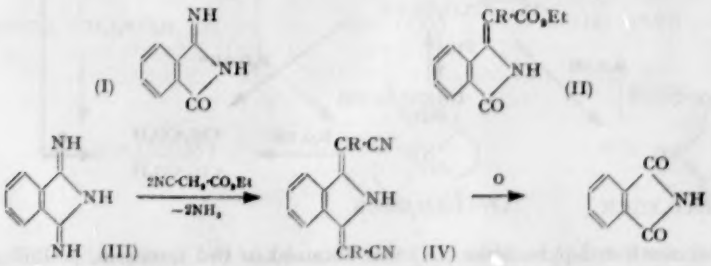
[15] Armbruster, *J. Amer. Chem. Soc.*, 1943, **65**, 1043.

50. *Heterocyclic Imines and Amines. Part VI.* Condensation Products from Di-iminoisoindoline and Succinimidine with Cyanoacetates.*

By J. A. Elvidge, John S. Fitt, and R. P. Linstead.

Di-iminoisoindoline (III) condenses with 2 mols. of ethyl cyanoacetate with elimination of 2 mols. of ammonia to give the *iso*indoline (IV; R = CO_2Et). Succinimidine (V) condenses with only 1 mol. of cyanoacetate to yield the pyrrolidine (VI), but in the presence of sodium ethoxide, it yields the di-condensation product (IX). Degradations and ozonolyses are described, light absorptions are given, and the structures of the compounds are discussed with particular reference to their unexpected properties.

The studies on imidines and their condensations with amines (previous papers * and forthcoming publications) have led to new syntheses of azaporphin pigments and related nitrogen-linked macrocycles (Elvidge and Linstead, *J.*, 1955, 3536; 1952, 5008; Linstead and Whalley, *J.*, 1955, 3530; Clark, Elvidge, and Linstead, *J.*, 1954, 2490). With the aim, ultimately, of preparing similar compounds containing carbon links, the condensation reactions of imidines with active methylene compounds are being investigated. Linstead and Rowe (*J.*, 1940, 1070) showed that the imine (I) condensed with acetoacetic and malonic ester, with elimination of ammonia, to yield the products (II; R = Ac and CO_2Et). The present paper is concerned mainly with analogous products from the reaction of cyanoacetates with di-iminoisoindoline (III) and with succinimidine (V).



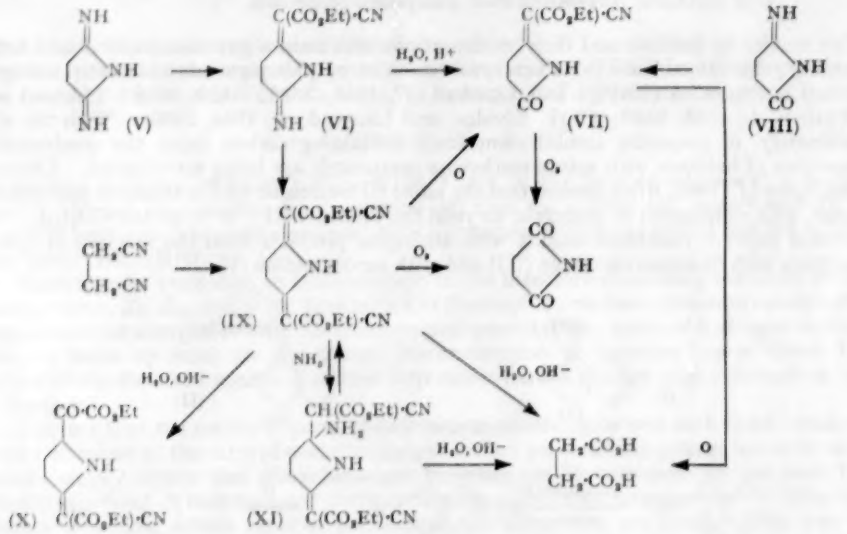
*iso*Indoline Derivatives.—Interaction of di-iminoisoindoline (III) with ethyl cyanoacetate in boiling ethanol produced ammonia and a yellow, dicondensation product, $C_{18}H_{18}O_4N_3$. That this (potentially tautomeric) compound had the structure (IV; R = CO_2Et) was confirmed by oxidation with permanganate to phthalimide in good yield. Incidentally, compound (IV; R = CO_2Et) was identified with a product prepared from phthalonitrile, guanidine, and ethyl cyanoacetate (Banfield, Thesis, Melbourne, 1950). Treatment of this compound (IV; R = CO_2Et) with alkali at once gave a red substance, presumably the resonance anion derived by deprotonation; this soon became hydrolysed, and after acidification the yellow dicarboxylic acid (IV; R = CO_2H) was isolated. Decarboxylation of the latter with pyridine and copper yielded 1 : 3-di(cyanomethylene)*iso*indoline (IV; R = H). This gave phthalimide in good yield on oxidation in conformity with the structure shown. The new *iso*indoline derivatives (IV) resisted acid hydrolysis and catalytic reduction. Their light absorptions are recorded in the Table.

Pyrrolidine Derivatives.—Succinimidine (V) differed from di-iminoisoindoline (III) in that it formed only a monocondensation product with ethyl cyanoacetate alone. The product, $C_9H_{11}O_2N_3$, was assigned the structure (VI) because of its light absorption (see

* Parts I—V, *J.*, 1952, 5000; 1953, 3593; 1954, 442; 1955, 3530.

Table) and its hydrolysis to the pyrrolidone (VII). This was synthesised from ethyl sodiocyanoacetate and iminosuccinimide (VIII), a compound of established constitution (Elvidge and Linstead, *J.*, 1954, 442). The imino-group of (VI) was unreactive to aniline, as well as to cyanoacetate, although it was readily hydrolysed. Attempts to oxidise the pyrrolidone (VII) with permanganate to succinimide produced gross decomposition. Ozonolysis, however, gave a 44% yield of succinimide.

The finding that iminosuccinimide (VIII) condensed with ethyl cyanoacetate only when the latter was presented as the sodio-derivative, prompted us to treat the imine (VI) with ethyl sodiocyanoacetate. This reaction yielded the 2 : 5-di(cyanoethoxycarbonylmethylene)pyrrolidine (IX), which was also obtained by a Thorpe condensation of succinonitrile with ethyl cyanoacetate in the presence of sodium ethoxide. The imine (VI) was not detected as an intermediate in this condensation.

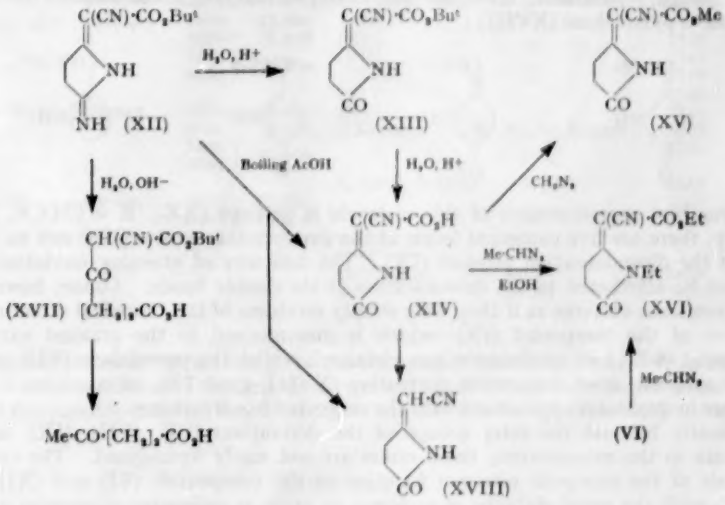


The disubstituted pyrrolidine (IX) was obtained in two forms, m. p. 150° and 205°. These were interconvertible by crystallisation (see Experimental section) and had identical light absorptions: they may be polymorphs or, less probably, *cis–trans*-isomers. The compound (IX) was weakly acidic, being sparingly soluble in concentrated aqueous ammonia, and it gave a monopotassio-derivative with potassium hydroxide in aqueous dioxan. The potassio-derivative decomposed when heated with water; clean hydrolysis to a carboxylic acid, as in the *iso*indoline series, was not obtained. Treatment of the potassio-derivative with dilute acid regenerated (IX) as a mixture of the two forms, m. p. *ca.* 171°. Attempted reaction of the potassio-derivative with ethyl iodide failed.

Like the monomethylenepyrrolidine (VI), the di(cyanoethoxycarbonylmethylene) compound (IX) resisted acid hydrolysis and proved troublesome to oxidise. From one oxidation of the latter, the pyrrolidone (VII) was isolated, whilst, more reliably, ozonolysis afforded some 6% of succinimide. Towards alkaline hydrolysis, the compound (IX) was unstable and tar was formed. Prolonged treatment with concentrated sodium hydroxide afforded succinic acid. Brief treatment, however, produced a crystalline product, $C_{12}H_{16}O_5N_2$, evidently derived by the replacement of a cyano- by a hydroxyl group. A possible structure is (X) or, perhaps better, the derived enol. The compound was acidic, gave a red colour with ferric chloride, and like simpler, highly enolised ketones failed to form ketonic derivatives (cf. Eisner, Elvidge, and Linstead, *J.*, 1951, 1501). It resisted mild acid hydrolysis and catalytic hydrogenation.

Treatment of the compound (IX) with dry ammonia afforded a 1 : 1 addition product, $C_{14}H_{18}O_4N_4$. This crystallised from acetic acid, and its light absorption, which differed from that of the potassio-derivative of (IX), indicated that the conjugation had been shortened (see Table). The preferred structure, therefore, is (XI); in agreement, the adduct was hydrolysed to succinic acid in good yield with aqueous alkali and was reconverted into the dimethylene compound (IX) when heated with benzoic anhydride. An adduct resembling (XI) was formed from the pyrrolidine (IX) and methylamine.

Because the ethyl ester groups of the pyrrolidine derivatives could not be hydrolysed selectively—there was either no attack or general decomposition—other esters were investigated. From methyl cyanoacetate and succinimidine, the methyl esters analogous to compounds (VI) and (VII) were prepared but these also were resistant to hydrolysis. Condensation of *tert.*-butyl cyanoacetate with succinimidine afforded the analogue (XII) which with hydrochloric acid in aqueous acetone gave the expected pyrrolidone (XIII). When the latter was boiled in aqueous acetic acid, *iso*butene was evolved and the oxo-

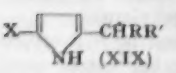


pyrrolidinecarboxylic acid (XIV) was formed. The structure of the acid was confirmed by the reaction with ethereal diazomethane which afforded the methyl ester (XV), identical with that from the condensation of methyl cyanoacetate with succinimidine. With diazoethane, the acid (XIV) reacted only when in solution (in ethanol) and then afforded a diethylated product. Since this was unaffected by primary amines it presumably has the structure (XVI) and is not the isomeric *O*-ether: less probably it has a *C*-Et structure. The same derivative (XVI) was obtained from the oxopyrrolidine ethyl ester (VII) and diazoethane in ethanol.

Attempts to remove only the *tert.*-butyl ester grouping of the parent imino-compound (XII) failed. Thus mild alkaline hydrolysis (cf. Barrett, Linstead, Leavitt, and Rowe, *J.*, 1940, 1076) effected more extensive degradation to an acid (XVII), $C_{11}H_{15}O_5N$, with loss of ammonia. The compound gave *iso*butene when heated in water, behaved as a dibasic acid on titration, gave an orange colour with ferric chloride, and was degraded to lævulic acid by acid hydrolysis. The acyclic keto-acid structure (XVII), doubtless highly enolised, therefore seemed most likely. In any case, the ultimate degradation product, lævulic acid, provided a confirmation of the carbon skeleton taken as present in the succinimidine–cyanoacetate condensation product (XII). Treatment of the imine (XII) with boiling acetic acid caused hydrolysis of the imino-group concomitantly with elimination of *iso*butene and some carbon dioxide: 5-cyanomethylene-2-pyrrolidone (XVIII) was isolated

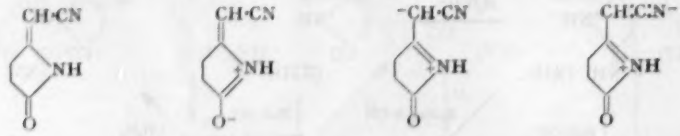
in every experiment, and sometimes also the acid (XIV). The oxopyrrolidine acid (XIV), best obtained from the ester (XIII), as mentioned above, was a little decomposed by sublimation but was decarboxylated satisfactorily to 5-cyanomethylene-2-pyrrolidone (XVIII) by boiling pyridine containing copper acetate.

Discussion of Structures.—The simple pyrrolidone (XVIII) gave succinimide in 79% yield on ozonolysis, a result which strongly supports the assigned bond structure, and thence of course the structures (XIV), (XIII), and (XII) for the precursors. This result is important because it excludes for these compounds the pyrrole structures (XIX). The evidence of light absorption (see Table) is not in disagreement (cf. Cookson, *J.*, 1953, 2789) though it is less clear-cut because of a lack of data for comparison.



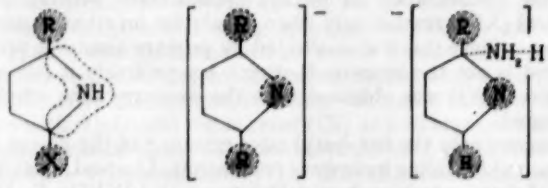
(XIX)
(X = NH_2, OH)

The properties of the compounds to which pyrrolidine structures have been given were unexpected. It seems that these might be accounted for (at least qualitatively) by regarding the compounds as resonance hybrids. Including bond structures which involve dipolar charge separations, there are for example four electronic isomers of 5-cyanomethylene-2-pyrrolidone (XVIII) :



Hence the best representation of this molecule is perhaps (XX; R = CH·CN, X = O). Similarly, there are five canonical forms of the oxopyrrolidine ester (VII) and no less than seven of the dicondensation product (IX). The difficulty of effecting oxidation cleanly may then be attributed to the delocalisation of the double bonds. Ozone, however, will attack resonance systems as if they were simply mixtures of the canonical structures. On ozonolysis of the compound (IX)—which is mesomerised to the greatest extent—the lowest yield (6·5%) of succinimide was obtained, whilst the pyrrolidone (VII) gave 44% and the simplest, least degenerate derivative (XVIII) gave 79% of succinimide. These results are in qualitative agreement with the suggested fine structures.

Evidently because the ester groups of the derivatives (VI), (VII), (IX), and (XV) participate in the mesomerism, these esters are not easily hydrolysed. The ready acid hydrolysis of the exocyclic nitrogen function of the compounds (VI) and (XII), which contrasts with the usual stability of amidines to acids, is indicative of electron deficiency at the adjacent carbon atom (position 2 of the ring). The resonance picture of the structures [see (XX)] shows there is such electron deficiency.



Region of electron excess. Region of electron deficiency.

The acidity of the pyrrolidones and of the dicondensation product (IX) is presumably a result of the localisation of positive charge in the neighbourhood of the pyrrolidine nitrogen [see (XX)]. This would facilitate the loss of a proton. In particular, the anion of the dicondensation product would have a lower energy content than the neutral molecule

(IX) because there are still seven canonical forms for the anion and none of these involves a formal separation of charges.

The resistance of the compounds to hydrogenation may result not only from the resonance stabilisation but also from steric hindrance. In acetic acid, with an active platinum catalyst, the compound (IX) was much more slowly hydrogenated than was benzene.

In contrast, ammonia added readily to the compound (IX). Under the reaction conditions, the disubstituted pyrrolidine (IX) was presumably present as the anion, and in this the negative charge would tend to have the distribution shown in (XXI) (derived by superposition of the seven hypothetical canonical forms). Interaction with ammonia, polarised in the sense $\overset{\delta-}{N}H_2-\overset{\delta+}{H}$, would give the anionic transition complex (XXII) from which the adduct (XI) would be derived.

Compound	Solvent	$\lambda_{max.}$ (Å)	ε	Compound	Solvent	$\lambda_{max.}$ (Å)	ε
(IV; R = CO_2Et)	$CHCl_3$	2800	13,600	(VI)	EtOH	3100	38,600
		3630 •	22,900	(XII)	,,	3100	34,300
		3960 }	30,300	(VII)	,,	2740	23,300
		4150 }		(XIII)	,,	2770	21,700
				(XIV)	,,	2730	25,200
(IV; R = CO_2H)	Dioxan	2550	16,300	(XVIII)	,,	2510	21,300
		3450	9,800	(IX) (both forms)	EtOH, hexane	3220	41,000
		3950 }	30,000			3320	43,000
		4150 }					
				K deriv. of (IX)	H_2O	3240	11,200
(IV; R = H)	Dioxan	2880	11,400			3350	12,900
		3590	28,400			3710	11,000
		3740	26,500				
				(XI)	AcOH	2830	30,600
				(X)	EtOH	2600	21,500
	• Inflection.			(XVII)	,,	2570	13,500

The light-absorption characteristics of the compounds (see Table) support the idea that the formal unsaturation and the functional groups are involved together in mesomerism. No one of the possible classical bond structures can account for the observed high-intensity maxima.

Experimental

Analyses are by Mr. F. H. Oliver and his staff of the microanalytical laboratory, and light-absorption measurements by Mrs. A. I. Boston of the spectroscopic laboratory of this Department.

1 : 3-*Di(cyanoethoxycarbonylmethylene)*iso*indoline* (IV; R = CO_2Et).—(a) ***Preparation.*** (i) Di-imino*iso*indoline (Elvidge and Linstead, *J.*, 1952, 5000) (21 g.) in methanol (1 l.) was heated under reflux with ethyl cyanoacetate (34 g.) overnight. The mixture was cooled and the yellow solid (44 g., 84%) collected. From ethyl methyl ketone, **1 : 3-*di(cyanoethoxycarbonylmethylene)*-iso*indoline*** formed long yellow needles, m. p. 231°, which showed a greenish fluorescence (Found : C, 64·0; H, 4·6; N, 12·2. $C_{18}H_{18}O_4N_2$ requires C, 64·1; H, 4·5; N, 12·5%).

(ii) [With Margaret Whalley] Guanidine (2·26 g.) was added to phthalonitrile (4 g.) in ethanol (40 c.c.), and the solution kept at 37° overnight. Ethyl cyanoacetate (8·7 g.) was added and the mixture warmed on the steam-bath for several minutes to start the reaction. Next day, the greenish solid product was extracted with ethanol. A trace of phthalocyanine (3 mg.) remained and from the extract di(cyanoethoxycarbonylmethylene)*iso*indoline (5 g.) was obtained as yellow crystals, m. p. 228—231° undepressed by the product from the preparation above (cf. Banfield, Thesis, Melbourne, 1950).

(b) ***Oxidation.*** A solution of di(cyanoethoxycarbonylmethylene)*iso*indoline (0·5 g.) in acetone (45 c.c.) was treated with potassium permanganate (1·5 g.) in water (20 c.c.) and, next day, with sulphur dioxide. The clear solution was evaporated to remove acetone, and the aqueous residue was cooled. Phthalimide (0·15 g., 80%) separated, m. p. and mixed m. p. 228°.

(c) ***Hydrolysis to the di-acid*** (IV; R = CO_2H). Addition of potassium hydroxide (10 g.) in water (750 c.c.) to di(cyanoethoxycarbonylmethylene)*iso*indoline (20 g.) dissolved in dioxan (1 l.)

afforded a dark red precipitate. This dissolved on warming of the mixture. The solution was then heated under reflux for 1 hr. and cooled, and the solid product was dissolved in the minimum of water. Acidification of the aqueous solution with hydrochloric acid precipitated 1 : 3-*di*-(*carboxycyanomethylene*)*iso*indoline (11 g., 66%; no characteristic m. p.) (Found: C, 60·0; H, 2·7; N, 15·0%; equiv., 139. $C_{14}H_7O_4N_3$ requires C, 59·8; H, 2·5; N, 14·9%; equiv., 140·6).

A solution of the potassium salt (0·25 g.) in water (30 c.c.) was kept overnight with potassium permanganate (1·5 g.). The mixture was then treated with acetone (30 c.c.) and sulphur dioxide, and the clear solution was evaporated, yielding phthalic acid (0·13 g., 90%), which was identified by mixed m. p. and by conversion into the *S*-benzylthiuronium salt.

1 : 3-*Di*(*cyanomethylene*)isoindoline (IV; R = H).—(a) *Preparation.* The di-acid (5 g.) and copper bronze (0·5 g.) were boiled together in pyridine (75 c.c.) for 1 hr. The filtrate was evaporated under reduced pressure, and the residue was powdered, mixed with charcoal, and extracted with ethanol in a Soxhlet apparatus. From ethanol, the 1 : 3-*di*(*cyanomethylene*)isoindoline (1·81 g., 53%) crystallised as long yellow needles (no m. p.) (Found: C, 74·4; H, 3·8; N, 21·8. $C_{12}H_7N_3$ requires C, 74·6; H, 3·65; N, 21·75%).

(b) *Oxidation.* Di(cyanomethylene)*iso*indoline (100 mg.) in acetone (40 c.c.), and potassium permanganate (0·6 g.) in water (5 c.c.), were shaken together overnight. The mixture was decolorised with sulphur dioxide, filtered, evaporated under reduced pressure to a small bulk, and cooled. The white solid (50 mg., 72%) which separated was identified as phthalimide by m. p. and mixed m. p.

5-*Cyanoethoxycarbonylmethylene*-2-*iminopyrrolidine* (VI).—Ethyl cyanoacetate (23·5 c.c.) was added to a boiling solution of succinimidine (Elvidge and Linstead, *J.*, 1954, 442) (19·7 g.) in ethanol (1 l.), and after 45 min. the mixture was cooled. Extractive crystallisation of the solid product (30 g., 76%) from pyridine afforded 5-*cyanoethoxycarbonylmethylene*-2-*imino*-*pyrrolidine* as a microcrystalline powder with no characteristic m. p. (Found: C, 55·9; H, 5·9; N, 21·7. $C_9H_{11}O_2N_3$ requires C, 55·95; H, 5·7; N, 21·75%). The imine dissolved in aqueous hydrochloric acid and was precipitated by ammonia or sodium hydroxide.

5-*Cyanoethoxycarbonylmethylene*-2-*pyrrolidone* (VII).—(a) *Preparation.* (i) A solution of the preceding imino-pyrrolidine (10 g.) in 3% hydrochloric acid (50 c.c.) was boiled until no more solid separated (6·3 g., 60%). Several crystallisations from ethanol afforded needles of 5-*cyano*-*ethoxycarbonylmethylene*-2-*pyrrolidone*, m. p. 140—150° unchanged by sublimation at 20 mm. (Found: C, 56·0; H, 5·4; N, 14·4. $C_9H_{10}O_3N_2$ requires C, 55·7; H, 5·2; N, 14·4%).

(ii) Ethyl cyanoacetate (1 g.) and iminosuccinimide (1 g.) were added successively to a cold solution of sodium ethoxide (from 0·3 g. of sodium) in ethanol (15 c.c.). The mixture was heated under reflux for 1 hr., cooled and poured into hydrochloric acid and ice. Recrystallisation of the precipitate from ethanol afforded 5-cyanoethoxycarbonylmethylene-2-pyrrolidone (0·8 g., 35%), m. p. 140—150° alone and in admixture with the previous preparation.

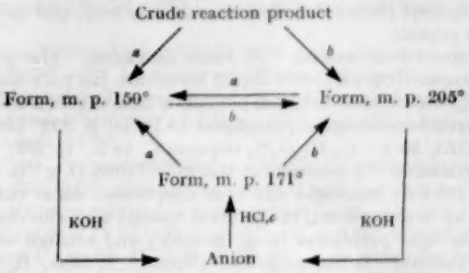
(b) *Oxidation.* Ozonised oxygen (1—3%) was bubbled slowly through a solution of 5-cyano-ethoxycarbonylmethylene-2-pyrrolidone (286 mg.) in acetic acid for 17 hr. Water (5 c.c.) was added and the solution evaporated on the steam-bath. The residue, which crystallised when rubbed with a glass rod, was drained on porous tile: the solid was identified as succinimide (65 mg., 44%) by mixed m. p.

2 : 5-*Di*(*cyanoethoxycarbonylmethylene*)*pyrrolidine* (IX).—(a) *Preparation.* (i) Ethyl cyano-acetate (3 g.) was added to cold ethanolic sodium ethoxide, prepared from sodium (1·2 g.) and ethanol (45 c.c.). 5-Cyanoethoxycarbonylmethylene-2-iminopyrrolidine (3 g.) was added, and the mixture was heated under reflux for 1 hr., cooled, and poured into ice (24 g.) and hydrochloric acid (12 g.). Recrystallisation of the greenish precipitate (3·7 g., 80%) from ethanol [charcoal or, better, brief treatment with permanganate, as in (d) (ii) below, to destroy impurities] afforded colourless needles, m. p. 205°, of 2 : 5-*di*(*cyanoethoxycarbonylmethylene*)*pyrrolidine* (Found: C, 58·1; H, 5·5; N, 14·3; OEt, 32·6. $C_{14}H_{15}O_4N_3$ requires C, 58·1; H, 5·2; N, 14·5; OEt, 31·1%). The compound was sparingly soluble in cold aqueous potassium hydroxide and in concentrated ammonia.

(ii) Succinonitrile (20 g.) was added to cold ethanolic ethyl sodiocyanoacetate, prepared from ethanol (75 c.c.), sodium (6 g.), and ethyl cyanoacetate (52 c.c.). The mixture was boiled for 1 hr. (ammonia was evolved), then cooled, and poured into ice (4·0 g.) and hydrochloric acid (80 g.). Recrystallisation of the greenish product (49 g., 53%) from ethanol (charcoal) gave colourless prismatic needles, m. p. 205° undepressed by the preceding preparation of 2 : 5-di-(cyanoethoxycarbonylmethylenep)yrrolidine. Crystallisation of the crude reaction product from light petroleum (b. p. 60—80°) gave prismatic needles, m. p. 150° (Found: C, 58·3; H, 5·5; N, 14·8%). Another sample, obtained from the potassio-derivative (see below) and

hydrochloric acid, was repeatedly crystallised from benzene–light petroleum (b. p. 60—80°); it then formed prismatic needles, m. p. 171° (Found: C, 58·2; H, 5·3; N, 14·7%). Mixtures of these forms of 2 : 5-di(cyanoethoxycarbonylmethylene)pyrrolidine had intermediate m. p.s.

The forms were interconverted quantitatively as follows:



a, 17 Hours' boiling with light petroleum (b. p. 60—80°).
b, 5 Hours' boiling with ethanol.
c, Crystallisation from benzene–light petroleum (b. p. 60—80°).

(b) *Potassio-derivative.* A hot solution of the pyrrolidine (IX) (1 g.) in dioxan (5 c.c.) was poured into a cold solution of potassium hydroxide (0·4 g.) in water (3 c.c.). After 10 min., the mixture was cooled in ice, and the solid was collected and washed exhaustively with ethanol. From cold pyridine (0·1% solution) by addition of light petroleum (b. p. 60—80°) (4 vols.) the *potassio-derivative* was obtained as small yellowish-brown prisms (Found: C, 51·8; H, 4·6; N, 12·9; K, 11·9. $C_{14}H_{14}O_4N_3K$ requires C, 51·4; H, 4·3; N, 12·9; K, 12·0%). This was sparingly soluble in water: no definite product could be isolated after the aqueous solution had been boiled.

After an attempt to cause the potassio-derivative to react with an excess of ethanolic ethyl iodide at 100° overnight, 2 : 5-di(cyanoethoxycarbonylmethylene)pyrrolidine (68%) was isolated, having m. p. and mixed m. p. 204°.

(c) *Acid-hydrolysis experiments.* The pyrrolidine derivative (IX) was recovered in >90, 85, and 50% yield respectively, after being heated with concentrated hydrochloric or 20% sulphuric acid under reflux, with 90% sulphuric acid at 40° for 48 hr., and with 4 : 10 : 1 sulphuric acid–acetic acid–water under reflux for 3 hr. Tar was formed under the last two sets of conditions and was the only product from an attempted hydrolysis with boiling 75% sulphuric acid.

(d) *Oxidations.* (i) Treatment of the pyrrolidine (IX) in 80% sulphuric acid with chromic acid produced hydrogen cyanide, carbon dioxide, and tar.

(ii) Treatment of the pyrrolidine (305 mg.) in acetic acid (20 c.c.) containing sulphuric acid (0·05 c.c.) with 0·1N-potassium permanganate solution (4 c.c., 2 atoms of O) afforded, after subsequent addition of sulphur dioxide and water (20 c.c.), a white solid (255 mg., 84%) which did not depress the m. p. of the high-melting form of the starting material (m. p. 205°) (Found: C, 58·4; H, 5·5%).

(iii) The pyrrolidine (IX) (1 g.) in acetone (50 c.c.) was stirred and slowly treated with potassium permanganate (1·5 g.) dissolved in the minimum of 5 : 1 acetone–water. The filtrate from the manganese dioxide was acidified, filtered, and evaporated to dryness. The residue crystallised from ethanol, affording 5-cyanoethoxycarbonylmethylene-2-pyrrolidone (75 mg., 12%), identified by mixed m. p.

(iv) Ozonised oxygen (1—3%) was slowly bubbled for 15 hr. through a solution of the pyrrolidine (IX) (1 g.) in acetic acid (30 c.c.). Water (10 c.c.) was added, the solution evaporated on the steam-bath, and the oily residue dried under reduced pressure over potassium hydroxide. Trituration of the residue with ethyl acetate afforded crystals which, after being drained on porous tile, were identified as succinimide (22 mg., 6·5%) by mixed m. p.

(e) *Action of alkali.* (i) The pyrrolidine (IX) (2 g.) was heated under reflux for 2 hr. with a solution of potassium hydroxide (3 g.) in water (10 c.c.) and ethanol (25 c.c.). The ethanol was removed by distillation in steam, and the solution was acidified (sulphuric acid), boiled for several minutes, and then extracted continuously with ether for 16 hr. Evaporation of the extract and crystallisation of the residue from water afforded succinic acid (0·4 g., 36%).

(ii) To the pyrrolidine (IX) (1 g.), suspended in boiling ethanol (8 c.c.), potassium hydroxide

(0·9 g.) in water (2 c.c.) was added. After 8 min., the ethanol was distilled off in steam, the solution was cooled and acidified, and the precipitate (0·25 g., 26%) collected. From ethanol (charcoal), *2-cyanoethoxycarbonylmethylene-5-ethoxalyl*(or *5-ethoxycarbonylhydroxymethylene*)-*pyrrolidine* (X) formed long needles, m. p. 136° (Found: C, 55·8; H, 5·9; N, 10·2; OEt, 29·1. $C_{12}H_{16}O_5N_2$ requires C, 55·7; H, 5·75; N, 10·0; OEt, 32·1). It behaved on titration with sodium hydroxide against phenolphthalein as a dibasic acid, and gave a red colour with ferric chloride in aqueous ethanol.

(f) *Addition products from amines.* (i) From ammonia. The pyrrolidine (IX) (5 g.) was dissolved in dry dioxan (100 c.c.), and liquid ammonia (25 c.c.) was added cautiously. The product (3·1 g., 58%) was crystallised from hot acetic acid to give *2-amino-2-cyanoethoxycarbonylmethyl-5-cyanoethoxycarbonylmethylenepyrrolidine* (XI), m. p. 232° (decomp.) (Found: C, 54·6; H, 6·1; N, 18·4; OEt, 30·1. $C_{14}H_{18}O_4N_4$ requires C, 54·9; H, 5·9; N, 18·3; OEt, 29·4%).

(ii) From methylamine. A solution of the pyrrolidine (1 g.) in dioxan (20 c.c.) was kept with methylamine (20 c.c.) overnight and then evaporated under reduced pressure. The dark product was taken up in chloroform, the solution treated with charcoal and evaporated, and the residue treated with light petroleum (b. p. 40—60°) and ethanol whereupon the *methylamine adduct* (20 mg.) crystallised; it had m. p. 241° (Found: C, 56·5; H, 6·5; N, 16·5. $C_{15}H_{20}O_4N_4$ requires C, 56·2; H, 6·3; N, 17·5%).

(iii) Alkaline hydrolysis of the ammonia product. A suspension of the compound (XI) (265 mg.) in 2N-sodium hydroxide (10 c.c.) was warmed on the steam-bath for 2 hr., during which ammonia was slowly evolved. Acidification of the solution and continuous extraction with ether for 24 hr. afforded succinic acid, which was crystallised from ethanol (yield, 70 mg., 68%; m. p. undepressed by an authentic specimen).

(iv) Action of benzoic anhydride on the ammonia product. The compound (XI) (255 mg.), mixed with benzoic anhydride (2 g.), was warmed on the steam-bath for 70 min., and the melt was then treated with 1 : 1 aqueous ammonia. From ethanol, the product afforded crystals (209 mg., 87%) of the high-melting form of 2 : 5-dicyanoethoxycarbonylmethylenepyrrolidine, identified by mixed m. p.

5-Cyanomethoxycarbonylmethylene-2-iminopyrrolidine.—(a) *Preparation.* Methyl cyanoacetate (1 c.c.) was added to a boiling solution of succinimidine (1 g.) in methanol (15 c.c.). After 1 hr., the mixture was cooled and the solid product (1·2 g., 60%) extractively crystallised from pyridine, to afford *5-cyanomethoxycarbonylmethylene-2-iminopyrrolidine* (Found: C, 53·7; H, 5·2; N, 23·3. $C_8H_9O_2N_3$ requires C, 53·6; H, 5·1; N, 23·45%).

(b) *Hydrolysis to the pyrrolidone* (XV). The preceding imine (1 g.) was boiled in 2N-hydrochloric acid for 10 min. and the solution was cooled. The product (0·35 g., 35%) was crystallised from methanol and sublimed under reduced pressure. *5-Cyanomethoxycarbonylmethylene-2-pyrrolidone* was obtained as needles, m. p. 167° (Found: C, 53·3; H, 4·3; N, 15·5. $C_8H_8O_3N_2$ requires C, 53·3; H, 4·5; N, 15·55%).

5-tert.-*Butoxycarbonylcyanomethylene-2-iminopyrrolidine* (XII).—*tert.*-Butyl cyanoacetate (Beech and Piggott, *J.*, 1955, 423) (10 g.) was added to a suspension of succinimidine (7·25 g.) in boiling *tert.*-butyl alcohol (350 c.c.). After 4 hr., the mixture was allowed to cool, and the product was collected, washed with methanol, and dried (yield, 13 g., 75%). The solid was extracted continuously with boiling pyridine and the solution treated with light petroleum (b. p. 80—100°). 5-tert.-*Butoxycarbonylcyanomethylene-2-iminopyrrolidine* was obtained as a microcrystalline powder, decomp. 238—240° (Found: C, 59·5; H, 7·1; N, 19·0. $C_{11}H_{15}O_2N_3$ requires C, 59·7; N, 6·8; N, 19·0%).

5-tert.-*Butoxycarbonylcyanomethylene-2-pyrrolidone* (XIII).—The preceding imine (1 g.) was boiled for 5 min. with a mixture of acetone (10 c.c.), water (9 c.c.), and concentrated hydrochloric acid (1 c.c.). When the mixture had cooled, the product (0·79 g., 78%) was filtered off. From aqueous ethanol, 5-tert.-*butoxycarbonylcyanomethylene-2-pyrrolidone* crystallised as needles, m. p. 174° (decomp.) (Found: C, 59·4; H, 6·5; N, 12·8. $C_{11}H_{14}O_3N_2$ requires C, 59·45; H, 6·35; N, 12·6%).

5-Carboxycyanomethylene-2-pyrrolidone (XIV).—(a) *Preparation.* The preceding pyrrolidone (XIII) (320 mg.) was boiled in 10% aqueous acetic acid (10 c.c.) until the evolution of *iso*butene slackened. When the solution was cooled, *5-carboxycyanomethylene-2-pyrrolidone* (100 mg., 42%) crystallised; it was recrystallised extractively from ether and then had m. p. 210° (decomp.) (Found: C, 50·4; H, 3·8; N, 16·8. $C_7H_6O_3N_2$ requires C, 50·6; H, 3·6; N, 16·9%).

(b) *Methylation.* An excess of ethereal diazomethane was added to a suspension of 5-carboxycyanomethylene-2-pyrrolidone (20 mg.) in ether (10 c.c.). After 30 min., the solution was evaporated to dryness and the residue sublimed at 130°/20 mm. The sublimate (8 mg.,

31%) was identified as 5-cyanomethoxycarbonylmethylene-2-pyrrolidone (above) by mixed m. p.

(c) *Ethylation.* An excess of ethereal diazoethane (Arndt and Scholz, *Z. angew. Chem.*, 1933, **46**, 47) was added to a solution of 5-carboxycyanomethylene-2-pyrrolidone (20 mg.) in ethanol (10 c.c.) and ether (10 c.c.). Evaporation of the solution and sublimation of the residue at 20 mm. afforded a white solid (23 mg., 86%), m. p. 65°, which did not depress the m. p. of material prepared as follows.

5-Cyanoethoxycarbonylmethylene-2-pyrrolidone (200 mg.), dissolved in ethanol (10 c.c.) and ether (10 c.c.), was treated with an excess of ethereal diazoethane. Subsequently, the solution was evaporated under reduced pressure and the residue sublimed at 20 mm. *5-Cyanoethoxycarbonylmethylene-1-ethyl-2-pyrrolidone* (XVI) (?) (201 mg., 87%) had m. p. 70° (Found: N, 13·0. $C_{11}H_{14}O_3N_2$ requires N, 12·6%).

Action of Alkali on 5-tert.-*Butoxycarbonylcyanomethylene-2-iminopyrrolidine.*—The imine (1 g.) was boiled with 2N-sodium hydroxide (10 c.c.) until it had just dissolved. Cooling of the solution and acidification with concentrated hydrochloric acid, precipitated 5-tert.-*butoxycarbonyl-5-cyano-4-oxopentanoic acid* (XVII) (1 g., 92%), m. p. 130° (Found: C, 55·1; H, 6·4; N, 6·2. $C_{11}H_{15}O_5N$ requires C, 54·8; H, 6·3; N, 5·8%). It dissolved in aqueous sodium hydrogen carbonate with effervescence, gave an orange colour with ferric chloride in aqueous ethanol, behaved as a dibasic acid on titration with sodium hydroxide against phenolphthalein, evolved *iso*butene on prolonged boiling with water, and failed to form ketonic derivatives (cf. Eisner, Elvidge, and Linstead, *J.*, 1951, 1501).

Degradation to Lævulic Acid.—When the acid (XVII) (1 g.) was boiled with concentrated hydrochloric acid, *iso*butene was evolved rapidly. After 3·5 hr., the solution was filtered from a little tar, cooled, and treated with an excess of a solution of 2 : 4-dinitrophenylhydrazine in concentrated hydrochloric acid. The dinitrophenylhydrazone of lævulic acid crystallised as orange-yellow needles (119 mg., 10%), m. p. and mixed m. p. 203°.

Action of Acetic Acid.—5-*tert.*-Butoxycarbonylcyanomethylene-2-iminopyrrolidine (0·7 g.) was boiled with 10% aqueous acetic acid (11 c.c.) until the evolution of *iso*butene became very slow. Tar was filtered off, and the solution was cooled.

(i) In two out of five runs, a white solid then separated (196 mg., 19%) which, after extractive crystallisation from ether, had m. p. 210° (decomp.) alone and when mixed with 5-carboxycyanomethylene-2-pyrrolidone (above).

(ii) Continuous extraction of the filtrate (charcoal) with ether and subsequent evaporation of the extract yielded crystals (55%), which were recrystallised from ethanol, and then sublimed at 150°/25 mm. The neutral, white, microcrystalline *5-cyanomethylene-2-pyrrolidone* (XVIII) had m. p. 170° (Found: C, 58·8; H, 5·2; N, 23·2. $C_6H_6ON_2$ requires C, 59·0; H, 4·95; N, 22·9%).

Decarboxylation of 5-Carboxycyanomethylene-2-pyrrolidone.—The cyano-acid (24·5 mg.) was boiled for 5 min. in pyridine containing copper acetate, the solution was evaporated under reduced pressure, and the residue sublimed at 20 mm. The neutral sublimate (10 mg.) was identified as 5-cyanomethylene-2-pyrrolidone (above) by mixed m. p.

At 210°/26 mm. the cyano-acid (19·8 mg.) afforded a slightly discoloured sublimate (9·8 mg.), soluble with effervescence in aqueous sodium hydrogen carbonate and having m. p. 200° undepressed by the starting material.

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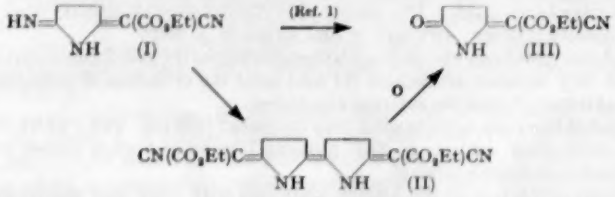
51. *Compounds containing Directly Linked Pyrrole Rings. Part I. A New Type of Pyrrole Pigment.*

By J. A. Elvidge, John S. Fitt, and R. P. Linstead.

A new magenta pigment, di-(5-cyanoethoxycarbonylmethylene-2-pyrrolidinylidene) (II), was formed in low yield when the iminopyrrolidine (I) was boiled in propionic acid and the solution kept at room temperature. On oxidation, the pigment took up *ca.* 1 mol. of oxygen and yielded 2 mols. of the pyrrolidone (III). The colour and fine structure of the compound are discussed, also its relation to indigo.

During attempts to remove, by ester exchange, the ethoxyl grouping of the pyrrolidine derivative [1] (I), the compound was treated with boiling propionic acid. A complex reaction occurred; the solution first darkened, and then during about 18 hr. at room temperature it became purple. Two strong absorption bands appeared at roughly 520 and 560 mμ. The formation of the pigment was reproducible.

The new pigment, present to the extent of only 1%, was isolated by chromatography on alumina and was crystallised extractively from benzene–light petroleum. It formed very dark red crystals with a brassy reflex. Molecular-weight estimations by the cryoscopic method in benzene, combustion analyses, and a Zeisel determination showed that the molecule was $C_{14}H_{10}O_2N_4(OEt)_2$. These figures correspond to condensation between



two molecules of the original pyrrolidine with loss of two imino-groups, so that the structure (II) appeared most probable. Oxidation of the pigment in acid solution with permanganate afforded approximately 2 mols. of the known pyrrolidone (III) with the consumption of 1 molecular proportion of oxygen. The structure (II) for the pigment was thus certain.

The mode of formation of the pigment (II) from the iminopyrrolidine (I) is at present obscure. The reaction may be a bimolecular reductive coupling. Evidence on this point is being sought and the production of analogous compounds by more rational procedures is under investigation.

The pigment was soluble in organic solvents (except petroleum), in hot concentrated hydrochloric acid, and in cold aqueous sodium hydroxide. It was rapidly and irreversibly destroyed by oxidising agents and by sodium dithionite (hydrosulphite).

The pigment in solution was practically transparent in the photographic ultraviolet and in the near infrared region but it absorbed light strongly in the yellow-green part of the visible region. The positions of the two absorption maxima were markedly affected by the solvent (see Table). The Figure gives the light absorption curve for the ethanol solution;

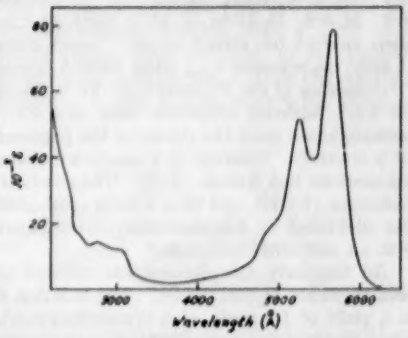
Solvent	$\lambda_{max.}$ (Å)	Colour of solution	U.V. Fluorescence
Ethanol	5240, 5630	Magenta	Pale green
Benzene	5400, 5810	Violet	Pale blue

the curve for benzene solution is very similar but is shifted 16—18 mμ to the red. In mixtures of these solvents, and in chloroform and nitrobenzene, the pigment showed maxima at intermediate wavelengths. Solutions in methanol, acetone, and acetic acid resembled that in ethanol, whilst a pyridine solution resembled that in benzene. Further observations of the light absorption indicated that the pigment formed loose complexes with

[1] Elvidge, Fitt, and Linstead, preceding paper.

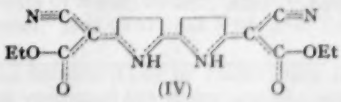
metal ions; maxima were: with copper or nickel acetate in pyridine, 6270 and 6230 Å, respectively; with sodium hydroxide in water, 6050 Å. Addition of acetic acid caused immediate decomposition of these complexes and there was reversion to the twin-peak (metal-free) spectrum.

The striking optical properties of the new pigment were not obviously compatible with the straightforward bond structure (II). Thus the simplest principles [2] suggested that the system would be equivalent to a linear hexaene for which the position of longest-wavelength absorption is 360 mμ (ε 70,000). The discrepancy between this prediction and observation is much greater than with the simpler pyrrolidine derivatives (I), (III), etc. (see ref. 1). Indigo, however, presents a good analogy for intense visual colour in a relatively simple structure. The light absorption at unexpectedly long wavelength by indigo is now attributed to resonance, the suggested canonical forms being the classical bond



Light absorption of the dipyrrolidinylidene (II) *in ethanol.*

structure, four dipolar forms and one tetrapolar form.[3] For the new pigment, the number of electronic isomers of the inadequate structure (II), comprising dipolar and tetrapolar forms of the kind invoked for the simple pyrrolidines [1] and for indigo, is no less than twenty-three. It is very reasonable, therefore, to regard the molecule of the new pigment as a resonance hybrid: it is perhaps best represented as (IV). The twenty-four canonical



(IV)

possibilities indicate that negative charge is carried over the extremities of the molecule and to a smaller extent at the centre, and that there is electron deficiency at the heterocyclic nitrogen atoms. In two-thirds of the hypothetical canonical forms the central link has full double-bond character: the oxidative scission to the pyrrolidone (III) in good yield is thus accommodated.

The changes in positions of the absorption maxima with solvent are similar to those encountered with indigo solutions.[4] Indeed, the effect is an expected characteristic of dyes which have easily polarisable molecules.[5] The suggested resonance-hybrid structure (IV) is certainly of this type.

The finding that an intensely coloured compound can result from the *direct linking* of two *partially reduced* pyrrolic rings as in (II) seems to be a new discovery in pyrrole chemistry.

Experimental

We are indebted to Mr. F. H. Oliver and his staff of the microanalytical laboratory of this Department for the analyses, including the direct determination of oxygen.

[2] Braude, *Ann. Reports*, 1945, **42**, 105.
[3] van Alphen, *Chem. Weekblad*, 1938, **35**, 435.
[4] Scheibe, Dörfling, and Assmann, *Annalen*, 1940, **544**, 240.
[5] Hünig and Rosenthal, *ibid.*, 1955, **592**, 161; Hünig and Requardt, *ibid.*, p. 180; cf. Kiprianov and Timoshenko, *Ukrain. khim. Zhur.*, 1952, **18**, 347.

Di-(5-cyanoethoxycarbonylmethylene-2-pyrrolidinylidene).—5-Cyanoethoxyçarbonylmethylene-2-iminopyrrolidine [1] (I) (4 g.), propionic acid (40 c.c.), and pyridine (1 c.c.) were heated together under reflux for 1 hr., and the dark solution was then kept at room temperature overnight. The purple mixture was diluted with benzene (100 c.c.) and filtered, and the solution run on to a column (90 × 6 cm.) of alumina (Spence, type H). The chromatogram was developed with benzene and when the bands ceased to move the column was kept overnight. During this time, a brown band, adjacent to the main violet-blue band of the pigment, changed to that colour. The several violet-blue bands were then eluted with 5% ethanol in benzene. The eluate was evaporated to 10 c.c., and light petroleum (b. p. 80—100°) (100 c.c.) was added. The pigment (25 mg., 0·7%) crystallised during *ca.* 3 hr. and was purified to constant light absorption by extractive crystallisation [6] with 20% benzene in light petroleum (b. p. 80—100°). *Di-(5-cyanoethoxycarbonylmethylene-2-pyrrolidinylidene)* formed small very dark red prisms with a slightly greenish, brassy reflex; it had no characteristic m. p. [Found: C, 61·0; H, 5·8; O, 18·1; N, 15·4; OEt, 24·2%; *M* (cryoscopic in benzene), 387 ± 50. $C_{18}H_{20}O_4N_4$ requires C, 60·7; H, 5·6; O, 17·9; N, 15·7; OEt, 25·3%; *M*, 356]. The pigment gave a dull purple smear when rubbed on glazed paper. Light absorption in EtOH: $\lambda_{max.}$ 5630, 5240 Å (ε 78,600, 51,400); in benzene, $\lambda_{max.}$ 5810, 5400 Å (ε comparable).

Oxidation of the Pigment.—(i) To a solution of the pigment (30 mg.) in glacial acetic acid (20 c.c.), aqueous sulphuric acid (0·3 c.c.; 1 : 1) was added, followed by 0·1N-potassium permanganate until the colour of the pigment was discharged [uptake of O, 1·3 mols. (corrected by a control). Scission of 1 aza-link between pyrrolic rings requires 0; one double bond, 1; one methine link 2 mols. of O]. The solution was evaporated to a small volume in an evacuated desiccator (KOH), and then a little crushed ice was added. The product (5 mg.) that separated was identified as 5-cyanoethoxycarbonylmethylene-2-pyrrolidone by m. p. and mixed m. p. with an authentic specimen.[1]

(ii) Similarly, the pigment was oxidised at 10 times the above dilution with 0·01N-potassium permanganate (1 mol. of O). The solution then had $\lambda_{max.}$ at 2750 Å with $E_{max.}$ corresponding to a yield of 1·9 mols. of 5-cyanoethoxycarbonylmethylene-2-pyrrolidone, a small quantity of which was isolated and identified as previously.

We gratefully acknowledge a maintenance grant awarded to J. S. F. by the Department of Scientific and Industrial Research.

DEPARTMENT OF CHEMISTRY, IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY, SOUTH KENSINGTON, LONDON, S.W.7. [*Received, July 8th*, 1955.]

[6] Barrett, Dent, and Linstead, *J.*, 1936, 1726.

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52. *Addition Reactions of Heterocyclic Compounds. Part II.* Phenanthridine and Methyl Acetylenedicarboxylate in Methanol.*

By R. M. ACHESON and G. J. F. BOND.

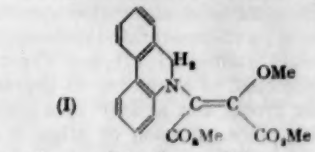
Phenanthridine and methyl acetylenedicarboxylate, in methanol containing varying amounts of water, gave three *N*-substituted phenanthridinium derivatives. Interconversions, and degradations to phenanthridine, phenanthridone, and to *N*-(1 : 2-*trans*-dicarbomethoxyvinyl)phenanthridone, provide structural proofs. Conversion of the last compound into an anhydride followed by hydrolysis gave the isomeric acid, which can only be the *cis*-isomer.

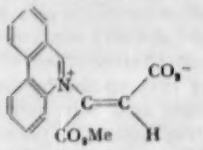
DIELS and THIELE [1] reported that equimolecular proportions of phenanthridine and methyl acetylenedicarboxylate reacted in methanol to give a high yield of a yellow compound, $C_{20}H_{19}O_5N$, containing three methoxyl groups. They proposed the 9 : 10-dihydrophenanthridine structure (I) for this compound by analogy with their erroneous structure [2] for

* The paper by Acheson and Burstall, *J.*, 1954, 3240, is considered as Part I.

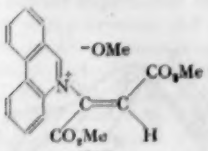
[1] Diels and Thiele, *J. prakt. Chem.*, 1940, **155—6**, 195.
[2] *Idem, Annalen*, 1939, **543**, 79.

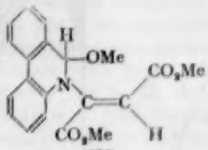
one of the acridine–methyl acetylenedicarboxylate–methanol adducts. Melting this yellow compound followed by crystallising the product from acetonitrile was alleged to give the *trans*-isomer. A colourless compound, $C_{18}H_{13}O_4N$, containing one methyl group and reported to be formed in 10% yield in the original condensation, was given a phenanthridinium formulation (II) and stated to give a hydrate on crystallisation from water. No degradative evidence was offered in support of these claims.

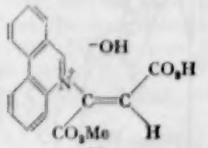

(I)


(II)

By analogy with the acridine–methyl acetylenedicarboxylate reaction which gives largely 10-(*trans*-1 : 2-dimethoxycarbonylvinyl)acridinium methoxide with a little of the *cis*-isomer,[3] the yellow compound from phenanthridine was thought to be probably 10-(*trans*-1 : 2-dimethoxycarbonylvinyl)phenanthridinium methoxide (III) or the conjugate 9 : 10-dihydrophenanthridine (IV). This formulation is not inconsistent with Diels and Thiele's data and has been verified.


(III)


(IV)


(V)

Phenanthridine and methyl acetylenedicarboxylate combined in anhydrous methanol to give a good yield of the yellow methoxide (III) alone. Crystallisation of this from methanol containing 5—15% of water gave exclusively and irreversibly the betaine (II or its isomer) whereas if the water content exceeded 15% the carboxyphenanthridinium hydroxide (V), Diels and Thiele's hydrate, was formed. The last two compounds were also obtained in excellent yield when the original condensation was carried out in the presence of the correct amounts of water, and were interconverted on crystallisation from the requisite aqueous methanol; it is clear that Diels and Thiele's methanol contained a few units per cent. of water.

Attempts to reconvert the betaine (II or its isomer) into the phenanthridinium methoxide (III) by boiling it with methanol left it unchanged; when the methanol contained some hydrogen chloride the ester group was hydrolysed. Attempts to esterify the betaine by diazomethane failed; both diazomethane and methyl diazoacetate gave cyclic compounds which may be dibenzopyrrocolines.

A phenanthridinium ethoxide could not be obtained crystalline from the methoxide (III) and dry ethanol—only a gum was isolated. Attempts to convert the methoxide (III) into the *cis*-isomer by boiling it with acetonitrile as described by Diels and Thiele also gave a gum.

Preparation of phenanthridine methiodide from phenanthridine with methyl sulphate in boiling nitromethane, followed by conversion into the iodide, was much more convenient than heating the base with methyl iodide in a sealed tube.[4] The ultraviolet absorption spectra of phenanthridine[5] and its hydrogen sulphate and of 10-methylphenanthridinium iodide in neutral and alkaline methanol[6] are shown in Figs. 1 and 2 and confirm earlier work. The considerable spectral differences between the phenanthridinium ion and the 9 : 10-dihydro-9-methoxyphenanthridine obtained with excess of sodium methoxide enable these species to be easily differentiated.

[3] Acheson and Burstall, *J.*, 1954, 3240.
[4] Pictet and Ankersmit, *Annalen*, 1891, **266**, 149.
[5] Cf. Badger and Pettit, *J.*, 1951, 3200.
[6] Cf. Tinkler, *J.*, 1906, **801**.

The ultraviolet absorption spectra of the phenanthridinium methoxide (III) in alkaline or neutral anhydrous methanol were identical and show (Fig. 1) that the compound is better represented as the 9 : 10-dihydro-9-methoxyphenanthridine (IV) under these conditions. The addition of acid changed the spectrum to the phenanthridinium-ion type (Fig. 2). The betaine (II or its isomer) has a phenanthridinium-ion spectrum in neutral and acid solution changing to that of the 9 : 10-dihydro-form on basification. The structure of the ionised hydroxide (V) is also supported by its ultraviolet absorption spectrum and by an infrared band at 5·95 μ confirming the presence of an $\alpha\beta$-unsaturated carboxyl group.

Proof of the constitution of one of the three phenanthridines (II, III, and V) establishes that of the other two, so the betaine (II) was subjected to a number of degradations. Boiling hydrochloric acid only hydrolysed the ester group, but at 200° in a sealed tube almost quantitative fission to phenanthridine took place. Fission of other *N*-alkyldihydrophenanthridines to phenanthridine under acid conditions has also been reported.[7]

FIG. 1. FIG. 2.

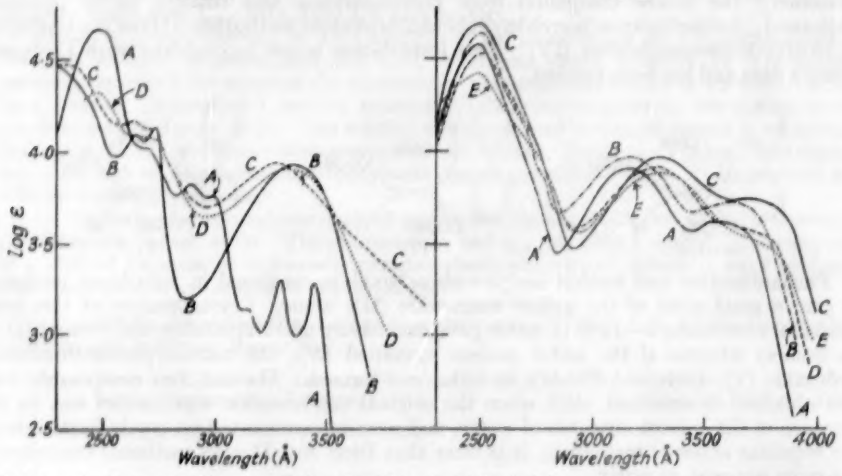


FIG. 1. *A, Phenanthridine in alkaline* MeOH. *B, N-Methylphenanthridinium iodide in alkaline* MeOH. *C, The methoxide in* MeOH. *D, The betaine in alkaline* MeOH.

FIG. 2. *A, Phenanthridine in acid* MeOH. *B, N-Methylphenanthridinium iodide in* MeOH. *C, The methoxide in acid* MeOH. *D, The betaine in* MeOH. *E, The hydroxide in* H_2O.

Refluxing the betaine with 20% aqueous potassium hydroxide also gave a good yield of phenanthridine, and oxidation with alkaline hydrogen peroxide gave phenanthridone. Hydrogenation over Raney nickel gave a dihydro-derivative, which contained 2 methoxy-groups but was not investigated fully, and then the side chain was split off with the formation of 9 : 10-dihydrophenanthridine; this was converted into the picrate which on crystallisation gave phenanthridine picrate, confirming other observations [7] on this easy oxidation. Several fruitless efforts were made to identify the other hydrogenation product. This type of reductive cleavage has also been reported in the acridine series [3] and these results leave no doubt that the side chain is attached only to the nitrogen atom.

Oxidation of the betaine (II) with alkaline ferricyanide to *N*-(*trans*-1 : 2-dicarboxyvinyl)phenanthridone proved this beyond all doubt. In refluxing acetic anhydride this acid was converted into the anhydride, which on hydrolysis gave the isomeric *N*-(*cis*-1 : 2-dicarboxyvinyl)phenanthridone, thus establishing the stereochemistry of these compounds and proving that the original condensation gave *trans*-products as is very largely the case also in the acridine series. It has not been possible to show if the carboxylate and the methoxycarbonyl group of the compound given structure (II) should be interchanged.

[7] Bates and Cymerman-Craig, *J.*, 1954, 1153.

Experimental

Infrared data refer to paraffin pastes and the *ca.* 3—7 μ region only.

Phenanthridine and Methyl Acetylenedicarboxylate.—(*a*) Methyl acetylenedicarboxylate (3·40 ml.) was added to a solution of phenanthridine (5·0 g.) in anhydrous methanol (40 ml.). After 48 hr. at room temperature the yellow precipitate (7·5 g., 76%) was collected and, crystallisation from methanol, gave yellow prisms of 10-(trans-1 : 2-*dimethoxycarbonylvinyl*)*phenanthridinium methoxide* (III), m. p. 108° (Found : C, 68·4; H, 5·4; N, 3·6; OMe, 26·5. $C_{20}H_{19}O_5N$ requires C, 68·0; H, 5·4; N, 4·0; 3OMe, 26·3%). Infrared maxima were at 5·78, 6·08, 6·21, 6·26, 6·46, 6·65, 6·71, 6·87, 6·96, and 7·12 μ.

(*b*) Repetition of experiment (*a*) but with methanol containing 5—15% of water gave an orange solid (7·2 g., 80%). Several recrystallisations from methanol gave colourless rhombs of the *betaine* (II), m. p. 180° (Found : C, 70·4; H, 4·1; N, 4·7; OMe, 11·0. $C_{18}H_{13}O_4N$ requires C, 70·4; H, 4·2; N, 4·6; 1OMe, 10·1%). Crystallisation from ethanol gave back the betaine (II), showing that the methoxy-group was non-ionic. With methanolic picric acid it gave a *semipicrate* which separated from methanol in yellow needles, m. p. 165° (Found : C, 59·4; H, 3·7; N, 8·7; OMe, 8·3. $C_{18}H_{13}O_4N,\frac{1}{2}C_6H_3O_7N_3$ requires C, 59·8; H, 3·4; N, 8·3; 1OMe, 7·4%). Infrared maxima of the betaine were at 5·79, 6·07, 6·18, 6·55, 6·70, 6·82, and 7·02 μ.

(*c*) A similar experiment but with methanol containing more than 15% of water gave a deposit of yellow crystals (6·5 g., 70%) which on crystallisation from the same solvent gave 10-(trans-x-*methoxycarbonyl*-x′-*carboxyvinyl*)*phenanthridinium hydroxide* (V) as pale yellow prisms, m. p. 154—155° (decomp.) (Found, after drying at 110° *in vacuo* : C, 66·0; H, 4·6; N, 4·4; OMe, 9·5. $C_{18}H_{15}O_5N$ requires C, 66·3; H, 4·6; N, 4·3; 1OMe, 9·5%), infrared maxima at 2·89, 3·05, 5·81, 5·95, 6·05, 6·17, 6·55, 6·69, 6·88, and 6·98 μ.

Cleavage of the Betaine (II) *to Phenanthridine.*—(*a*) The betaine (1 g.) was refluxed with concentrated hydrochloric acid (20 ml.) for 10 min. The clear golden-yellow solution first formed soon deposited a colourless solid (0·85 g.) which when crystallised from methanol gave the *betaine* of 10-(1 : 2-dicarboxyvinyl)phenanthridinium hydroxide as a colourless microcrystalline powder, m. p. 205° (Found : C, 69·0; H, 3·8; OMe, 0·0. $C_{17}H_{11}O_4N$ requires C, 69·5; H, 3·8; OMe, 0·0%).

(*b*) Basification of the clear yellow solution obtained by heating the betaine (II) (1 g.) with concentrated hydrochloric acid (5 ml.) in a sealed tube to 200° for 3 hr. gave a white precipitate (0·5 g., 90%). Crystallisation from aqueous methanol gave colourless needles, m. p. and mixed m. p. 104°, of phenanthridine.

(*c*) The betaine (II) (2·0 g.) was refluxed for 2 hr. with 20% aqueous potassium hydroxide (20 ml.). Phenanthridine (0·9 g., 80%), which separated, had m. p. and mixed m. p. 104° (from aqueous methanol).

Hydrogenation of the Betaine (II).—The betaine (2·0 g.) in methanol (150 ml.) was shaken with Raney nickel under hydrogen at room temperature and pressure for 12 hr., 2 mols. being absorbed. Filtration gave a solution with a strong blue-violet fluorescence, and addition of hot picric acid (1·5 g.) in methanol (5 ml.) gave an orange precipitate of 9 : 10-dihydrophenanthridine picrate (2·3 g., 85%). Crystallisation from dioxan gave yellow needles, m. p. and mixed m. p. 240° with phenanthridine picrate; the infrared absorptions of the specimens were identical. Evaporation of the methanol solution, obtained by repeating the above hydrogenation but omitting the picric acid stage, gave only a gum.

Oxidation of the Betaine (II).—(*a*) The betaine (1 g.), methanol (40 ml.) and 30% aqueous hydrogen peroxide (1 ml.) were heated on a steam-bath for 30 min. and then left at room temperature for 48 hr. Evaporation to dryness, extraction of the residue with ether, and evaporation of the extract gave phenanthridone (0·35 g., 50%) which yielded colourless needles, m. p. and mixed m. p. 293°, from aqueous ethanol.

(*b*) The betaine (1·0 g.) in hot 10% aqueous potassium hydroxide (10 ml.) was treated with potassium ferricyanide (2·5 g.) in hot water (5 ml.) and left on a steam-bath for 3 hr. After filtration from a trace of phenanthridone (0·01 g.), acidification precipitated 10-(trans-1 : 2-*dicarboxyvinyl*)*phenanthridone* (0·89 g.), which, after several recrystallisations from water (charcoal) separated in pale yellow prisms, m. p. 261—263° (decomp.) (Found : C, 66·5; H, 4·1. $C_{17}H_{11}O_5N,1\frac{1}{2}H_2O$ requires C, 60·6; H, 4·2. Found, after drying at 110° *in vacuo* : C, 66·5; H, 3·8; N, 4·7. $C_{17}H_{11}O_5N$ requires C, 66·0; H, 3·6; N, 4·5%). The infrared absorption spectrum of the *hydrate* had maxima at 2·90, 4·00, 5·8—5·9, 6·02, 6·25, 6·37, 6·90, and 6·99 μ.

This acid (0·9 g.) was refluxed with acetic anhydride (2 ml.) for 30 min. The product which was precipitated on cooling crystallised from acetic anhydride, giving the ***anhydride*** as yellow needles, m. p. 196—197° (Found: C, 70·1; H, 3·3; N, 4·7. $C_{17}H_9O_4N$ requires C, 70·1; H, 3·1; N, 4·8%), infrared maxima at 3·25, 5·46, 5·67, 5·95, 6·15, 6·24, 6·75, 6·90, and 6·98 μ.

The anhydride was dissolved in just sufficient warm aqueous sodium hydroxide. Acidification with hydrochloric acid precipitated **10-(cis-1 : 2-*dicarboxyvinyl*)*phenanthridone dihydrate*** which crystallised from water in colourless rhombs, m. p. 179—180° (yellow at 110—130°) (Found: C, 59·1; H, 4·3; N, 4·1. $C_{17}H_{11}O_5N,2H_2O$ requires C, 59·0; H, 4·4; N, 4·65%). Drying at 110—120° over P_2O_5 *in vacuo* gave the acid anhydride, identical in m. p. and infrared absorption spectra with an authentic specimen. Infrared maxima of the acid dihydrate were at 2·96, 3·9, 5·8—5·85, 6·05, 6·23, 6·36, 6·90, and 6·98 μ (shoulder).

Reaction of the Betaine (II) *with Diazo-compounds.*—(*a*) The betaine (3·0 g.) in methanol (200 ml.) was treated with diazomethane (0·4 g.) in ether (20 ml.). Nitrogen was evolved and evaporation yielded a solid *substance* (2·5 g.) which crystallised from methanol in orange prisms, m. p. 222° (Found: C, 70·8; H, 4·9; N, 4·3; OMe, 9·9. $C_{19}H_{15}O_4N$ requires C, 71·0; H, 4·7; N, 4·3; 1OMe, 9·7%), which may be a dibenzo[*eg*]pyrrocolinium betaine.

(*b*) The betaine (2·0 g.) in methanol (150 ml.) was treated with methyl diazoacetate (1·3 g.). Evaporation and crystallisation of the residue yielded mainly the original betaine, but from its mother-liquor a red solid (0·2 g.) was obtained. Crystallisation from methanol yielded red prisms of a *substance* (analogous to the above pyrrocoline), m. p. 179° (Found: C, 66·4; H, 4·7; N, 3·5; OMe, 16·0. $C_{21}H_{17}O_6N$ requires C, 66·4; H, 4·5; N, 3·6; 2OMe, 16·3%).

10-Methylphenanthridinium Iodide.—Phenanthridine (2·0 g.) in nitromethane (10 ml.) and methyl sulphate (2·0 g.) were refluxed for 1 hr., cooled, and diluted with dry ether (50 ml.). The hygroscopic precipitate was treated in water (15 ml.) with potassium iodide (6·0 g.) in hot water (6 ml.), 10-methylphenanthridinium iodide (3·43 g., 96%) being precipitated. Crystallisation from methanol gave orange rhombs (3·1 g.), m. p. 202—203° (Pictet and Ankersmit[4] give m. p. 200°).

We thank Mr. M. L. Burstall for his interest in this work, and Mr. A. O. Plunkett for valuable technical assistance.

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THE LABORATORY OF HUMAN NUTRITION, DEPARTMENT OF BIOCHEMISTRY,
OXFORD. [*Received, August 16th*, 1955.]

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53. *The Optical Stability of* 1 : 2 : 3 : 4-*Tetrahydro-2-naphthylamine.*

By ALWYN G. DAVIES, E. E. EDWIN, and J. KENYON.

Pope and Harvey's report[1] that 1 : 2 : 3 : 4-tetrahydro-2-naphthylamine racemises during liberation from its salts, or during the preparation of its derivatives, has been examined. The base has been resolved as its hydrogen (+)-tartrate, and it is shown that the (+)- and the (−)-bromocamphorsulphonate of the amine used by the above-mentioned authors contain some two-thirds of the amine in its racemic form; it was probably this racemic material initially present that led to the isolation of partially racemised crystalline derivatives. In the present work no evidence of optical instability was obtained.

MANY examples are recorded in the literature of the racemisation of alcohols, esters, and other alkyl–oxygen compounds in which the oxygen atom is attached to the asymmetric centre of the molecule. This has been interpreted in terms of unimolecular alkyl–oxygen heterolysis, and has contributed much to our understanding of this subject.[2]

Relatively few examples of the analogous racemisation of amines are known. Although the optical instability of derivatives of α-amino-acids can clearly be ascribed to the ionisation of the α-hydrogen atom, a few examples remain where the reason for it is not obvious. At the outset of the present work the best authenticated case appeared to be in the report by

[1] Pope and Harvey, *J.*, 1901, **79**, 74.
[2] Davies and Kenyon, *Quart. Rev.*, 1955, **9**, 203.

Pope and Harvey,[1] reiterated by Cloetta and Waser,[3] that 1 : 2 : 3 : 4-tetrahydro-2-naphthylamine is extensively racemised during its liberation from its salts and during reaction at the nitrogen atom. To determine the mechanism of the process which causes optical instability in the amine, and its chemical consequences, we have examined this report.*

By treating the amine (2 mols.) with ammonium (+)- or (−)-3-bromocamphor-8-sulphonate (1 mol.), Pope and Harvey obtained the (+)-amine (+)-bromocamphorsulphonate, $[\alpha]_D$ +86·5° (in EtOH), and the (−)-amine (−)-bromocamphorsulphonate, $[\alpha]_D$ −86·2° (in EtOH); the resolution was therefore assumed to be complete. Treatment of the salt of the (+)-amine with alkali gave, in separate experiments, the (+)-amine, α_D +30·5° and +37·24°. The active bromocamphorsulphonates were then converted, usually *via* the free base, into a number of solid derivatives, which, in every case, could be separated by fractional crystallisation into racemic and optically active fractions. The maximum rotatory powers of particular active fractions were: hydrochloride, $[\alpha]_D$ +71·9° and −69·7° (in H_2O); (+)-amine (+)-camphor-10-sulphonate, +47·7°, and (−)-amine (−)-camphor-10-sulphonate, −47·4° (in H_2O); by use of the principle of the additivity of the molecular rotations of the anion and cation of a salt, these compounds were shown probably to be optically pure. Pope and Harvey concluded that partial racemisation occurred during liberation of the base from its salts, and that more extensive racemisation accompanied the preparation of the derivatives. They ascribed this behaviour to the ionisation of the α-hydrogen atom. Cloetta and Waser [3] found difficulty in crystallising the (+)-bromocamphorsulphonate of the amine, and so resolved the base by the use of ½ mol. of (+)-tartaric acid. The resulting salt had $[\alpha]_D$ +57·8° (in H_2O) and gave the hydrochloride, $[\alpha]_D$ +43·64° (in H_2O). These authors stated that the formation of the hydrochloride is accompanied by partial inversion.

We have resolved 1 : 2 : 3 : 4-tetrahydro-2-naphthylamine as its hydrogen tartrate formed from equimolecular amounts of the base and of (+)-tartaric acid. After recrystallisation from water the most active salt had $[\alpha]_D$ +86° (in H_2O) and gave successively the amine α_D +95·83° (undiluted), and (without its isolation) the amine hydrochloride, $[\alpha]_D$ +67·5° (in H_2O) raised to +71·9° by recrystallisation from water. This corresponds well with Pope and Harvey's maximum values of +71·9° and −69·7°; it is therefore probably safe to assume, as these authors do, that this amine hydrochloride is optically pure. The rotatory power of the optically pure amine may therefore be calculated to be about 102°.

No loss of optical activity was observed when the amine was recovered after prolonged treatment in solution with sodium ethoxide, sodium hydroxide, or excess of hydrochloric acid. Similarly when the amine was dissolved in acid and liberated with alkali successively four times, it was recovered with undiminished optical activity. Again, the use of sodium carbonate or of sodium ethoxide in the decomposition of the hydrogen tartrate did not alter the rotatory power of the amine obtained.

We therefore prepared the (+)-bromocamphorsulphonate from our active hydrochloride and hydrogen tartrate in order to repeat Pope and Harvey's original experiments, and obtained products with $[\alpha]_D$ +101° and +102° (in EtOH). In aqueous solution the corresponding values are $[\alpha]_D$ +86° and +87°, respectively. Assuming the additivity of the molecular rotations of the anion ($[M]_D$ +277°) [1] and cation ($[M]_D$ +132°)[1, 5] of the salt in dilute aqueous solution, we derive $[M]_D$ +409° for optically pure (+)-1 : 2 : 3 : 4-tetrahydro-2-naphthylammonium (+)-bromocamphorsulphonate, whence $[\alpha]_D$ = +89° (in H_2O). This confirms the substantial optical purity of our specimens, as would be expected if no racemisation occurred during their preparation.

The above (+)-bromocamphorsulphonate, $[\alpha]_D$ +101 to +102° (in EtOH), is to be

* Pickard and Kenyon [4] found that the corresponding 1 : 2 : 3 : 4-tetrahydro-2-naphthol is optically stable and does not undergo unimolecular alkyl–oxygen heterolysis. These results have been confirmed and extended by Barratt (unpublished work).

[3] Cloetta and Waser, *Arch. exp. Pathol. Pharmakol.*, 1913, **73**, 398.
[4] Pickard and Kenyon, *J.*, 1912, **101**, 1427.
[5] See p. 253.

compared with that of $[\alpha]_D$ +86·5° and −86·2° which Pope and Harvey assumed to be optically pure, and upon which they performed their experiments. The probability therefore immediately arises that the inactive compounds which they isolated by fractional crystallisation of derivatives of the amine were not formed by racemisation during reaction, but were derived from racemic base present in the incompletely resolved bromocamphorsulphonate. This has been confirmed by performing the cycle of operations

amine ⟶ hydrochloride ⟶ bromocamphorsulphonate ⟶ amine

avoiding fractional crystallisation of any of the intermediate salts, whereupon the amine was recovered with undiminished optical activity.

Pope and Harvey considered this possibility that their original bromocamphorsulphonates might be partially racemic, but claimed to have disproved it by finding racemisation in the cycle of reactions camphorsulphonate ⟶ amine ⟶ camphorsulphonate. Unfortunately no details of this experiment are given and we have not detected any racemisation during these reactions. To confirm that fractionation had not occurred during the final isolation of our camphorsulphonate the cycle amine ⟶ camphorsulphonate ⟶ amine was performed, isolation of the salt being avoided. No racemisation was observed. The camphorsulphonate from our most active (+)-amine had $[\alpha]_D$ +46·3° (in H_2O) which compares well with Pope and Harvey's maximum values, and therefore, as these authors assumed, probably represents optical purity.

Why Pope and Harvey, in separate experiments, obtained amine of varying rotatory power from the same specimen of bromocamphorsulphonate, which forms part of their evidence for the occurrence of racemisation, is not clear. The rotatory power of the amine varies with temperature but not sufficiently to account for this large difference, and, although the amine rapidly forms a carbonate in the air, we have shown that this exerts only a small effect on the rotatory power of the amine.

We conclude therefore that, whereas Pope and Harvey probably obtained the amine hydrochlorides and camphorsulphonates optically pure, the bromocamphorsulphonates, upon whose reactions they based their conclusions of optical instability, were only about one-third resolved. In all probability the racemic solid, which they isolated from the active derivatives by recrystallisation, was derived from the two-thirds of inactive amine initially present and was not formed during reaction. It is unfortunate that they did not investigate similarly the reactions of their hydrochlorides or camphorsulphonates, or isolate the liquid amine rather than its solid derivatives, or measure the optical rotatory power of their bromocamphorsulphonates in aqueous solution rather than in ethanol; any of these experiments would have indicated the source of their racemic product.

We have obtained no evidence of optical instability.

Experimental

(+)-1 : 2 : 3 : 4-*Tetrahydro-2-naphthylammonium Hydrogen* (+)-*Tartrate*.—The (±)-amine (80 g., 1 mol.) in acetone (*ca.* 125 c.c.) was added to a solution of (+)-tartaric acid (80 g., 1 mol.) in water (125 c.c.). Next day the thick mass of crystals was separated, washed with 50% aqueous acetone (50 c.c.) and with acetone (50 c.c.) and dried *in vacuo* (yield, 126 g.). Nine recrystallisations from water gave the salt, m. p. 217°, $[\alpha]_D^{18}$ +86° (*l*, 1; *c*, 0·4360 in H_2O).

(+)- *and* (−)-1 : 2 : 3 : 4-*Tetrahydro-2-naphthylamine*.—(i) The above hydrogen (+)-tartrate (5 g.) was shaken for a few min. with 50% aqueous potassium hydroxide (10 c.c.). The liberated base was extracted with ether, and the extract washed and dried ($MgSO_4$), yielding the (+)-amine (2·2 g.), b. p. 115°/*ca.* 12 mm., α_D^{20} +96·0° (*l*, 1; undild.), α_{5461}^{19} +115·40°, α_{5892}^{19} +95·83°, α_{6438}^{19} +75·88° (*l*, 1; undild.).

(ii) A sample of the (−)-amine hydrogen (+)-tartrate (5 g.) $[\alpha]_D^{20}$ −12° (*l*, 1; *c*, 2·632 in water), which was recovered from the mother-liquors of the resolution, was warmed for 20 min. (steam bath) with a solution of sodium carbonate (5 g.) in water (100 c.c.). More sodium carbonate (15 g.) was added and the free base extracted by the usual procedure; it had α_D^{24} −33·73° (*l*, 0·5; undild.).

(iii) A further sample of the same hydrogen tartrate as in (ii) was suspended in ethanol (40 c.c.) containing sodium ethoxide (from 4 g. of sodium). After the mixture had refluxed

for 0·5 hr., water (20 c.c.) was added, and most of the ethanol distilled off. Extraction of the residue with ether gave the amine, α_D^{24} −35·20° (*l*, 0·5; undild.). The difference in rotatory power between these two samples is probably not significant.

From the amine, α_D +81·20° (*l*, 1; undild.), were prepared the *N*-(1 : 2 : 3 : 4-tetrahydro-2-naphthyl)dithiocarbamate, m. p. 142°, $[\alpha]_D^{22}$ +62° (*l*, 1; *c*, 0·466 in EtOH) [Bamberger and Müller [6] report m. p. 142° for the (±)-compound], and *N*-(1 : 2 : 3 : 4-tetrahydro-2-naphthyl)-thiourea, m. p. 195°, $[\alpha]_D^{22}$ +84° (*l*, 1; *c*, 0·557 in EtOH) (Found: C, 64·5; H, 7·25; N, 13·5; S, 15·55. Calc. for $C_{11}H_{14}N_2S$: C, 64·0; H, 6·85; N, 13·6; S, 15·55%).

(+)-1 : 2 : 3 : 4-*Tetrahydro-2-naphthylammonium Carbonate.*—In contact with air the amine forms a crust of the carbonate in a few minutes,[6] and much more slowly becomes coloured through oxidation. (It may be inferred that this difficulty influenced Pope and Harvey's choice in basing their evidence for racemisation on the rotatory power of the amine's solid derivatives, rather than that of the amine itself.) Before the optical rotations of specimens of the amine were measured the polarimeter tubes (capillary, end-filling), capillary-teat pipette, and rubber teat were always flushed with nitrogen; similarly, specimens of the amine were always sealed under nitrogen. With rapid work and these precautions, no formation of carbonate was apparent. The effect of a small amount of carbonate on the rotatory power of the amine was determined as follows:

Solid carbon dioxide was added to a solution of a few drops of the amine, α_D^{18} +81·20° (*l*, 1·0; undild.), in ether. The thick white precipitate of carbonate was separated and dried *in vacuo* at room temperature; it had $[\alpha]_D^{21}$ +92° (*l*, 1; *c*, 0·4570 in EtOH), +78° (*l*, 1; *c*, 0·922 in CH_2Cl_2), α_D^{20} +80·42° (*l*, 1; *c*, 0·844 in the amine of α_D^{18} +81·20°). The presence of a small amount of the carbonate therefore has little effect on the rotatory power of the amine.

(+)-1 : 2 : 3 : 4-*Tetrahydro-2-naphthylammonium Chloride.*—The amine (0·2894 g.), α_D^{19} +95·83 (*l*, 1; undild.), was dissolved in 0·231N-hydrochloric acid (8·52 c.c., 1·00 equiv.), and the solution diluted to 10 c.c.; it then had $[\alpha]_D^{20}$ +67·5° (*l*, 1), whence the ratio of $[\alpha]$ for the amine hydrochloride to α for the amine is +0·704. This value was duplicated in a second experiment. The presence of a few drops of concentrated hydrochloric acid did not change this rotation. By recrystallisation from water a less soluble fraction of the hydrochloride was obtained, having $[\alpha]_D^{17}$ +72° (*l*, 1; *c*, 1·293 in H_2O).

Optical Stability of the Amine to Acid and Base.—(i) *Hydrochloric acid.* A solution of the optically impure (+)-amine hydrochloride (0·2502 g.) in water (25 c.c.) containing concentrated hydrochloric acid (1·0 c.c.) had α_D +0·46° (*l*, 1). This value was unchanged after the sample had been kept for 3 days in the dark.

(ii) *Sodium ethoxide.* The amine (5 g.), α_D +52·10° (*l*, 1; undild.), was dissolved in a solution of sodium (0·05 g.) in ethanol (10 c.c.). Next day water was added and the amine was recovered, b. p. 120°/15 mm., α_D +51·70° (*l*, 1; undild.).

(iii) *Sodium hydroxide.* The amine (3 g.) which was isolated from (ii) was dissolved in a solution of sodium hydroxide (2 g.) in *ca.* 95% ethanol. After 2 weeks the amine was recovered, α_D +51·92° (*l*, 1; undild.).

Optical Stability during Repeated Formation and Decomposition of the Amine Hydrochloride.—The amine (4 g.), α_D −68·93° (*l*, 1; undild.), was dissolved in 50% hydrochloric acid (10 c.c.), and the solution then made alkaline with 50% aqueous potassium hydroxide to liberate the amine. Acid and alkali were added in turn till the salt had been formed three times and decomposed three times. At each stage the pH of the solution was checked with Universal indicator. The amine finally recovered (*ca.* 2 g.) had b. p. 120°/15 mm., α_D −68·90° (*l*, 1; undild.).

(+)-1 : 2 : 3 : 4-*Tetrahydro-2-naphthylammonium* (+)-*Bromocamphorsulphonate.*—(i) *From the hydrochloride.* A saturated aqueous solution of ammonium (+)-3-bromocamphor-8-sulphonate (0·35 g.) was added to a solution of the amine hydrochloride (0·2 g.), $[\alpha]_D$ +72° (*l*, 1; *c*, 1·293 in H_2O), in water (10 c.c.). The amine (+)-bromocamphorsulphonate soon separated as needles, which were washed with water and dried *in vacuo*; they had $[\alpha]_D^{14}$ +86° (*l*, 1; *c*, 0·895 in H_2O), $[\alpha]_D^{17}$ +101° (*l*, 1; *c*, 1·071 in EtOH).

(ii) *From the hydrogen* (+)-*tartrate.* On mixing hot saturated aqueous solutions of the hydrogen (+)-tartrate, $[\alpha]_D^{18}$ +82° (*l*, 1; *c*, 0·4360 in H_2O), and of ammonium (+)-bromocamphorsulphonate (1·1 g.), the (+)-bromocamphorsulphonate of the amine separated after about 30 sec.; it was isolated as described above; it (0·86 g.) then showed m. p. 188·5—190°, $[\alpha]_D^{20}$ +87° (*l*, 1; *c*, 0·3676 in H_2O).

(iii) *From the amine.* Ethereal solutions of (+)-bromocamphorsulphonic acid and of the

[6] Bamberger and Müller, *Ber.*, 1888, **21**, 847.

amine, α_D +84·8° (*l*, 1; undild.), were mixed; the salt which separated had $[\alpha]_D^{20}$ +81° (*l*, 1; *c*, 1·142 in H_2O).

The Cycle Amine ⟶ Hydrochloride ⟶ Bromocamphorsulphonate ⟶ Amine.—The amine (2·2 g.), α_D^{14} +84·8° (*l*, 1; undild.), in ether (10 c.c.) was treated with an excess of ethereal hydrogen chloride whereupon the amine hydrochloride was quantitatively precipitated. When aqueous solutions of this hydrochloride and of ammonium (+)-bromocamphorsulphonate were mixed, the (+)-bromocamphorsulphonate of the amine immediately separated. After 1 hr. the solid and supernatant liquid were jointly treated with an excess of 50% potassium hydroxide solution, and the amine was recovered; it had α_D^{13} +83·64° (*l*, 1; undild.).

(+)-1 : 2 : 3 : 4-*Tetrahydro-2-naphthylammonium* (+)-*Camphorsulphonate.*—The amine (0·5 g.), α_D^{20} +96·8° (*l*, 1; undild.), in ethanol (5 c.c.) was mixed with (+)-camphor-10-sulphonic acid (0·8 g.) in ethanol (2 c.c.). The camphorsulphonate separated on being kept; it was washed with alcohol and with ether and dried at 100°/16 mm.; it had m. p. 219·5—220·5°, $[\alpha]_D^{20}$ +46·3° (*l*, 1; *c*, 2·243 in H_2O), $[\alpha]_D^{20}$ +70·5° (*l*, 1; *c*, 0·921 in EtOH).

The Cycle Camphorsulphonate ⟶ Amine ⟶ Camphorsulphonate.—A mixture of the above-mentioned (+)-amine (+)-camphorsulphonate (0·6 g.), $[\alpha]_D^{20}$ +46·3° (in H_2O), and an excess of 20% sodium carbonate solution was kept at 60° for a few minutes. The liberated amine was collected in ether and treated with a solution of (+)-camphorsulphonic acid (0·36 g.) in ethanol. After 2 hr. the (+)-amine (+)-camphorsulphonate was filtered off, washed with ether, and dried at 100° *in vacuo*; it (0·4 g.) had $[\alpha]_D^{20}$ +46·8° (*l*, 1; *c*, 2·820 in H_2O).

The Cycle Amine ⟶ Camphorsulphonate ⟶ Amine.—The amine (1·0 g.), α_D^{20} +81·2° (*l*, 1; undild.), in ether was shaken with (+)-camphorsulphonic acid (1·6 g.) in water. The ether was boiled off, leaving a homogeneous solution from which the (+)-amine (+)-camphorsulphonate separated on cooling. After 4 days the crystals and supernatant liquid were jointly treated with an excess of 2N-sodium hydroxide, yielding the amine, α_D^{20} +80·58° (*l*, 1; undild.).

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54. *Studies in Aromatic Nucleophilic Substitution. Part IV.* Relative Nucleophilic Powers of Common Reagents.*

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Relative reactivities of a series of reagents of widely differing nucleophilic power towards an aromatic carbon atom have been measured in absolute methanol. Arrhenius parameters are recorded. The results show the necessity for the analysis of products in any attempt to correlate such relative rates. The reactivity of the thiophenoxide ion is discussed.

The original statement by Hughes, Ingold, and Patel [1] that for replacement reactions, $Y + R{-}X \longrightarrow Y{-}R + X$, basicity is a sufficient indication of the nucleophilic power of Y was a close enough approximation to develop the theory of such replacement reactions. Later, numerous experimental results have shown that relative nucleophilic powers towards Lewis acids and protons do not normally follow the same sequence. Swain and Scott [2] and Edwards [3] have set up equations designed to correlate rates of nucleophilic displacements and equilibrium data. On the matter of displacements at an aromatic carbon atom, the data are limited: an approximate order of nucleophilic powers was drawn up by Bunnett and Zahler [4] and supplemented by Bunnett and Davis.[5] The results to be discussed are an attempt to document such relative reactivities under standard conditions.

* Parts I—III, *J.*, 1951, 2340; 1953, 655; 1954, 3091.

[1] Hughes, Ingold, and Patel, *J.*, 1933, 526.
[2] Swain and Scott, *J. Amer. Chem. Soc.*, 1953, **75**, 141.
[3] Edwards, *ibid.*, 1954, **76**, 1540.
[4] Bunnett and Zahler, *Chem. Rev.*, 1951, **49**, 273.
[5] Bunnett and Davis, *J. Amer. Chem. Soc.*, 1954, **76**, 3011.

Since a number of reactions have been studied in methanol or ethanol the solvent used was absolute methanol. A preliminary account has been given.[6] Results are assembled in Tables 1 and 4.

TABLE 1. k_2 (*l. sec.*$^{-1}$ *mole*$^{-1}$) *for reaction of* p-*fluoronitrobenzene with* X *in absolute methanol.*

X	SPh$^-$			$C_6H_5\cdot NH_2$		
Temp.	35·07°	49·72°	60·08°	149·5°	158·6°	168·4°
k_2	$5{\cdot}01 \times 10^{-4}$	$2{\cdot}17 \times 10^{-3}$	$5{\cdot}67 \times 10^{-3}$	$1{\cdot}28 \times 10^{-4}$	$1{\cdot}82 \times 10^{-3}$	$2{\cdot}55 \times 10^{-3}$

TABLE 2. k_2 (*l. sec.*$^{-1}$ *mole*$^{-1}$) *for reaction of picryl chloride with* X *in absolute methanol.*

X	$C_6H_5\cdot NH_2$			m-$NO_2\cdot C_6H_4\cdot NH_2$		
Temp.	−22·04°	−16·71°	−10·80°	4·00	25·06°	35·12°
k_2	$5{\cdot}65 \times 10^{-3}$	$7{\cdot}72 \times 10^{-3}$	$1{\cdot}11 \times 10^{-1}$	$5{\cdot}54 \times 10^{-4}$	$2{\cdot}29 \times 10^{-3}$	$4{\cdot}15 \times 10^{-3}$
X	Cl$^-$			MeOH		
Temp.	34·52°	49·80°	59·99°	35·06°	49·76°	67·70°
k_2	$2{\cdot}42 \times 10^{-4}$	$1{\cdot}31 \times 10^{-3}$	$4{\cdot}02 \times 10^{-3}$	$6{\cdot}39 \times 10^{-7}$	$2{\cdot}47 \times 10^{-6}$	$1{\cdot}08 \times 10^{-5}$

TABLE 3. k_2 (*l. sec.*$^{-1}$ *mole*$^{-1}$) *at 25° and Arrhenius parameters* ($k_2 = Be^{-E/RT}$).

Reaction of X with :	*p*-fluoronitrobenzene				picryl chloride			
X	OMe$^-$ [a]	SPh$^-$	OPh$^-$ [b]	$C_6H_5\cdot NH_2$	$C_6H_5\cdot NH_2$	m-$NO_2\cdot C_6H_4\cdot NH_2$	Cl$^-$	MeOH
k_2	1·80 ×10^{-4}	1·68 ×10^{-4}	~10^{-6}	$1{\cdot}56 \times 10^{-6}$	$6{\cdot}77 \times 10^{-5}$	$2{\cdot}27 \times 10^{-3}$	7·40 ×10^{-6}	7·55 ×10^{-9}
log B	11·0	10·7	—	2·11	5·59	5·34	11·5	6·64
E	20·1	19·8	—	13·5	7·86	10·9	22·7	18·1

(*a*) Bevan and Bye, *J.*, 1954, 3091; (*b*) England, *Chem. and Ind.*, 1954, 1145.

TABLE 4. k_2 (*l. sec.*$^{-1}$ *mole*$^{-1}$) *at 25° for reaction of* p-*fluoronitrobenzene with* X.

X	OMe$^-$	SPh$^-$	OPh$^-$	$C_6H_5\cdot NH_2$	m-$NO_2\cdot C_6H_4\cdot NH_2$	Cl$^-$	MeOH
k_2	$1{\cdot}80 \times 10^{-4}$	$1{\cdot}68 \times 10^{-4}$	~10^{-6}	$1{\cdot}56 \times 10^{-6}$	$5{\cdot}23 \times 10^{-13}$	$1{\cdot}71 \times 10^{-14}$	$1{\cdot}74 \times 10^{-17}$

DISCUSSION

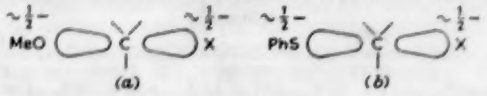
In Table 4 are shown rate constants for the reaction of various nucleophiles X with *p*-fluoronitrobenzene, calculated on the assumption that the relative rates for aniline with the latter and with picryl chloride are preserved for other nucleophiles X. It is probable that in the latter case the steric requirements of the two *o*-nitro-groups in initial and transition states are such as to make the last three values of Table 4 only approximations to the actual value of k_2 for the reaction of *p*-fluoronitrobenzene with X. However, it is unlikely that such effects will invalidate the calculated order of reactivity, which corresponds closely to that set up approximately by Bunnett and Zahler [4] with one important exception. The thiophenoxide ion, from our data, has a reactivity very close to that of the methoxide ion, contrary to experience of their relative reactivities at an aliphatic carbon atom; cf. references in Bevan and Hirst,[6] where the difference is ~10^3 in favour of the thiophenoxide ion. The closeness of the figures for OMe$^-$ and for SPh$^-$ suggested the possibility that the equilibrium

$$Ph\cdot SH + MeO^- \rightleftharpoons Ph\cdot S^- + MeOH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

lies well to the left. However, rate constants determined by following decrease in concentration of sulphide ion, and separately of alkalinity, corresponded exactly and the reaction product was almost pure 4-nitrodiphenyl sulphide. Further, Hammett [7] gives the autoprotolysis constant of methanol at 25° as pK = 16·7, and Hine and Brader [8] give for the

[6] Bevan and Hirst, *Chem. and Ind.*, 1954, 1422.
[7] Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, 1940, p. 256.
[8] Hine and Brader, *J. Amer. Chem. Soc.*, 1953, **75**, 3964.

thiophenol in methanol a value of $pK_a = 11{\cdot}6$. From these figures it can be shown that in (1), under the conditions used, Ph·SH is more than 97% converted into PhS^-. This means that MeO^- is a considerably stronger base than PhS^-. The transition states for attack by these two ions may be represented by (*a*) and (*b*). Evidently in (*b*) the negative charge



(*a*) (*b*)

can be moved further away by resonance in the benzene ring, with a consequent lowering of transition-state energy (*cf.* Swain and Scott [9]). However, if this were the only factor involved then the phenoxide ion should be more reactive than the methoxide ion, and the *p*-nitrophenoxide ion even more so: but this is not found experimentally. A conflicting factor is the availability at the attacking centre of the electron pair involved in partial-bond formation, balanced against the internuclear repulsion term. Thus $\geqslant C{-}S^-$, being more polarisable than $\geqslant C{-}O^-$, can form a partial bond at greater internuclear distance than the latter, with a consequent lowering of transition-state energy, accounting for the greater reactivity observed for the aliphatic ion.

However, in the transition state of aromatic substitution, in which it is fairly generally agreed that the reactive carbon atom is approximately tetrahedral, in order to form partial bonds both $\geqslant C{-}O^-$ and $\geqslant C{-}S^-$ must approach close to the tetrahedral bond distance; thus the latter loses its advantage of being able to form a partial bond at relatively greater internuclear distance. The driving force of the weaker S–C partial bond is less than that of the O–C bond, with a consequent levelling in the reactivities of the two ions.

In the exchange reaction of chloride ion with picryl chloride it was found that methanolysis occurs slowly and that the final product is picric acid. The concentration of chloride ion produced by the reaction

$$C_6H_2(NO_2)_3Cl + CH_3{\cdot}OH \longrightarrow C_6H_4(NO_2)_3{\cdot}O{\cdot}CH_3 + Cl^- + H^+$$

rises to a maximum and then falls rapidly to zero. This is evidently due to cleavage of the 2 : 4 : 6-trinitroanisole by chloride ion: $C_6H_2(NO_2)_3{\cdot}O{\cdot}CH_3 + Cl^- + H^+ \longrightarrow C_6H_2(NO_2)_3{\cdot}OH + CH_3Cl$. Initial rates for the exchange reaction were measured while methanolysis had not occurred to more than a few units %.

The results in Tables 3 and 4 show that, although the parallel between nucleophilic power and basicity is overall a useful guide, the application of this principle within a fairly narrow range of relative reactivity requires detailed consideration of the various transition states involved.

Experimental

Materials.—p-*Fluoronitrobenzene.* This was prepared from fluorobenzene by Swarts's method [9] and separated from the *ortho*-isomer by fractionation at 20 mm.; it had m. p. 21—21·5° (labile form).

Picryl chloride. This was prepared by the method of Boyer *et al.*; [10] it had m. p. 83·5°.

Aniline. A commercial sample, shaken with zinc dust and distilled at 16 mm., had b. p. 76° (uncorr.).

m-*Nitroaniline.* A commercial sample, recrystallised from benzene, had m. p. 114·5—115° (uncorr.).

Thiophenol. A commercial sample was distilled, and the middle fraction used.

Methanol. Magnesium (10 g.) and iodine (0·5 g.) were dissolved in "AnalaR" methanol (2 l.), which was then refluxed for ½ hr. and distilled.

Kinetic Measurements.—Thermostat temperatures below 100° were steady to within ±0·02°; those above 100° to within ±0·05°.

(1) *Reaction of methoxide ion with* p-*fluoronitrobenzene.* Bevan's procedure [11] was used

[9] Swarts, *Rec. Trav. chim.*, 1913, **33**, 263.
[10] Boyer, Spencer, and Wright, *Canad. J. Res.*, 1946, **24**, *B*, 202.
[11] Bevan, *J.*, 1953, 655.

except that the indicator was bromocresol-green–methyl-red. For the reaction at 49·66°, $k_2 = 2{\cdot}38 \times 10^{-3}$ l. sec.$^{-1}$ mole^{-1}; Bevan and Bye [12] gave for this temperature $k_2 = 2{\cdot}39 \times 10^{-3}$ l. sec.$^{-1}$ mole^{-1}.

(2) *Reaction of thiophenoxide ion with* p-*fluoronitrobenzene.* The reaction was followed by two methods: measurements of (*a*) the reduction in alkalinity, by acid titration; (*b*) the disappearance of thiophenoxide ion, by reaction with iodine.

Initially, in (*b*) the constants obtained were 10—11% higher than in (*a*) and the infinity titre corresponded to more thiophenoxide consumed than was required by theory. This was attributed to oxidation of thiophenoxide ion to disulphide and was eliminated by conducting the reaction in an atmosphere of nitrogen.

Thiophenol was weighed into a flask, and the flask flushed with oxygen-free nitrogen. Sodium methoxide solution was added, leaving a 5% excess of thiophenol. The reaction tubes were flushed with nitrogen, and aliquot portions of a standard solution of *p*-fluoronitrobenzene in methyl alcohol added. The tubes were cooled in ice, nitrogen bubbled through for a further 20 sec. to remove dissolved air, and aliquot parts of thiophenoxide solution added. The tubes were sealed and placed in the thermostat. The reaction was stopped by plunging the tubes into ice-water. In method (*a*), the contents of the tubes were added to an excess of standard hydrochloric acid plus 10 c.c. of benzene, and the excess of acid back-titrated with sodium hydroxide (methyl-red–bromocresol-green indicator). In (*b*), the contents of a tube were added to 25 c.c. of N-hydrochloric acid, solid potassium iodide was added followed by a known volume of standard potassium iodate solution, and the excess of iodine titrated with sodium thiosulphate. The light green colour which developed in "infinity" tubes was probably due to the formation of a trace of nitroso-compound. Results are given below.

Determination of k_2 (*l. sec.*$^{-1}$ *mole*$^{-1}$) *for reaction of* p-*fluoronitrobenzene with* SPh^- *in absolute methanol.*

Method (*b*). Initially, [Halide] = 0·03087N, [SPh^-] = 0·06395N. Temp. 49·72°.
Concns. in ml. of 0·01988N-$Na_2S_2O_3$ solution per 10·04 ml. sample.

t (sec.)	0	36	45	55	65	75	85	95	105	116
[Ph·SNa]	31·07	27·61	27·03	26·32	25·6	24·83	24·53	23·65	23·13	22·55
[Halide]	15·28	11·82	11·24	10·53	9·82	9·04	8·74	7·86	7·34	6·76
10^3k_2	—	2·05	1·99	1·99	2·04	2·13	2·02	2·20	2·22	2·27

Mean $k_2 = 2{\cdot}11 \times 10^{-3}$. By method (*a*), $k_2 = 2{\cdot}13 \times 10^{-3}$.

(3) *Reaction of* p-*fluoronitrobenzene with aniline.* This reaction was followed by Chapman and Parker's method.[13] The results are annexed. Corrected for solvent expansion on the assumption that the figures for methanol [14] may be extrapolated to higher temperatures, $k_2 = 2{\cdot}18 \times 10^{-5}$.

Determination of k_2 (*l. sec.*$^{-1}$ *mole*$^{-1}$) *for reaction of* p-*fluoronitrobenzene with aniline in absolute methanol.*

Initially, [Fluoride] = 0·015M, [Aniline] = 0·06M. Temp. 158·6°.
Concns. in ml. of 0·02022N-$Na_2S_2O_3$ per 5·06-ml. sample.

t (hr.)	0	43·91	57·41	59·01	60·76	67·93	73·5	83·3	93·68
[Aniline]	90·20	86·64	85·96	85·56	85·72	85·63	85·08	84·44	83·64
[Halide]	21·71	18·15	17·47	17·07	17·23	17·14	16·59	15·95	15·15
10^5k_2	—	1·93	1·80	1·94	1·81	1·66	1·75	1·78	1·86

Mean $k_2 = 1{\cdot}82 \times 10^{-5}$.

(4) *Reaction of picryl chloride with aniline.* The reaction was very rapid at −20° so the following technique was used. Portions (5 ml.) of standard methanol solutions of aniline and picryl chloride in stoppered test-tubes were brought to thermostat temperature. For "initial" readings, the contents of an aniline tube were poured into one of picryl chloride, the tube was restoppered and shaken, and the contents were quickly poured into 25 ml. of acetone and 2 ml. of concentrated nitric acid. Chloride ion liberated was titrated potentiometrically by silver nitrate. For other readings the same procedure was used on tubes which, after being shaken, were re-immersed in the thermostat for a definite time.

[12] Bevan and Bye, *J.*, 1954, 3091.
[13] Chapman and Parker, *J.*, 1951, 3301.
[14] Timmermans, "Physico-chemical Constants of Pure Organic Compounds," Elsevier, New York, 1950, p. 30.

In this reaction, as for the analogous reaction of *m*-nitroaniline, 2 mols. of amine are consumed per mol. of halide; hence the equation for the second-order rate constant is

$$k_2 = [2{\cdot}303/2t(0{\cdot}5a - b)]\log_{10}b(0{\cdot}5a - x)/0{\cdot}5a(b - x)$$

The results follow.

Determination of k_2 (l. sec.$^{-1}$ mole^{-1}) for reaction of picryl chloride with aniline in absolute methanol

Initially, [Picryl chloride] = 0·02702N, [Aniline] = 0·1201N. Temp. −10·80°.
Concns. in ml. of 0·0100N-$AgNO_3$ per 10-ml. sample.

t (sec.)	0	22·0	30·0	46·0	52·0	65·0	76·0
[Aniline]	56·71	50·97	49·41	46·79	46·02	44·52	42·79
[Halide]	23·70	17·96	16·40	13·78	13·01	11·51	9·78
$10k_2$	—	1·17	1·16	1·15	1·14	1·12	1·20

Mean $k_2 = 1{\cdot}16 \times 10^{-4}$; duplicate, $1{\cdot}15 \times 10^{-4}$.

(5) *Reaction of* m-*nitroaniline with picryl chloride.* Standard solutions of the two reagents in methanol were brought to thermostat temperature, and equal volumes mixed. Portions (10 ml.) were withdrawn at intervals, run into 20 c.c. of *ca.* 2N-nitric acid, and the chloride ion titrated potentiometrically with silver nitrate. The results are tabulated below.

Determination of k_2 (l. sec.$^{-1}$ mole^{-1}) for reaction of picryl chloride with m-*nitroaniline in absolute methanol.*

Initially, [Halide] = 0·02999N, [Amine] = 0·1200N. Temp. 4·00°.
Concns. in ml. of 0·009986N-$AgNO_3$ per 10-ml. sample.

t (min.)	0	72	93	113	133	153	169	191	211	267	295	331	358
[Amine]	59·06	52·07	50·40	49·25	47·86	46·65	45·90	44·84	44·04	41·94	40·76	39·75	39·07
[Halide]	29·37	22·38	20·71	19·56	18·17	16·96	16·21	15·15	14·35	12·25	11·07	10·06	9·39
10^4k_2	—	5·70	5·76	5·60	5·70	5·75	5·69	5·69	5·64	5·60	5·76	5·74	5·72

Mean $k_2 = 5{\cdot}69 \times 10^{-4}$; duplicate, $5{\cdot}62 \times 10^{-4}$.

(6) *Exchange reaction between picryl chloride and radioactive chloride ions.* An approximately 0·35N-aqueous solution of radioactive lithium chloride was evaporated to dryness, and the residue strongly heated and allowed to cool in a stream of dry air. Absolute methanol was quickly added, and the flask tightly stoppered. Two methods were used to follow the exchange reaction.

(*a*) Methanolic solutions (10 ml. each) of radioactive lithium chloride and of picryl chloride were placed in separate limbs of an "H" tube, which was then placed in a thermostat; and after attaining thermostat temperature the contents of the two limbs were mixed, the time of mixing being taken as zero, and the tube left in the thermostat for a known interval. Reaction was stopped by immersing the tube in ice-water and washing the contents into a mixture of 20 ml. of chloroform and 40 ml. of distilled water. After extraction and separation, the aqueous layer was extracted twice with 20 ml. of chloroform, the aqueous layer was evaporated to dryness, and the solid obtained dissolved in 15 ml. of distilled water; 10 ml. of the latter solution were pipetted into a counter, and the radioactivity measured by use of standard scaling equipment. The total chloride ion in a 10-ml. sample was estimated by Volhard's method.

(*b*) The two standard solutions (100 ml. of each) were mixed, and 20-ml. portions sealed in tubes and placed in the thermostat. Initial tubes were taken at zero time, and thereafter tubes were removed at known intervals. The run was stopped by plunging the tubes into ice-water, and the methanol was removed by suction. The residue was dissolved in 20 ml. of benzene and 10 ml. of water, the aqueous layer extracted with a further 20 ml. of benzene, the volume made up to 20 ml. with distilled water, and the solution evaporated to a small bulk and finally made up to 15 ml. with distilled water. The specific activity was then found as in (*a*). Blank runs with picryl chloride showed that no appreciable hydrolysis took place in either extraction technique.

If a and b are the concentrations of picryl chloride and lithium chloride, and if c and $c - x$ are the specific activities of the initial lithium chloride and the salt obtained from a reaction stopped after time t, then the second-order constant is given by the equation (cf. le Roux and Sugden [18]).

$$k_2 = [2{\cdot}303/t(a + b)] \log_{10} [1 - x(1 + b/a)/c]^{-1}$$

[18] le Roux and Sugden, *J.*, 1939, 1279.

This formula is valid when no exchange has taken place at $t = 0$, *i.e.*, as in technique (*a*). When exchange has proceeded at $t = 0$, as in (*b*), then if the specific activities at $t = 0$ and $t = t$ are x_1 and x_2, the equation becomes

$$k_2 = \frac{2{\cdot}303}{(a+b)t} \cdot \log_{10}\left\{\left[1 - \frac{x_1}{c}\left(1 + \frac{b}{a}\right)\right]\left[1 - \frac{x_2}{c}\left(1 + \frac{b}{a}\right)\right]^{-1}\right\}$$

Determination of k_2 (l. sec.$^{-1}$ mole^{-1}) for the reaction of picryl chloride with radioactive chloride ion.

Initially, [Picryl chloride] = 0·00975M, [LiCl*] = 0·04193M. Temp., 59·99°.
Concns. in ml. of 0·03436N-NH_4CNS per 10-ml. sample.

t (min.)	0	40	60	70	80	90
[Counts/min.]	626	524·3	501·4	499·4	536·5	564·5
[Concn. of Cl^- ion]	15·4	14·18	14·10	14·36	15·64	15·44
10^4k_2	—	4·05	3·85	3·87	3·68	3·86

Mean $k_2 = 3{\cdot}86 \times 10^{-4}$.
Corrected for solvent expansion, $k_2 = 4{\cdot}02 \times 10^{-4}$.

(7) *Methanolysis of picryl chloride.* This reaction was followed by potentiometric measurement of the chloride ion produced in aliquot parts of standard methanolic picryl chloride immersed in a thermostat for definite periods of time. The chloride-ion concentration rose to a maximum depending on the temperature at which the run was carried out and then fell rapidly to zero. Rate constants calculated on the basis of the chloride-ion concentration produced fell off slowly with time, and that for methanolysis was taken as that determined by extrapolation of initial rate measurements to zero time.

Determination of k_1 (solvolysis) for picryl chloride in absolute methanol.

Initially, [Picryl chloride] = 0·02987M. Temp. 35·06°.
Concns. in ml. of 0·01823N-$AgNO_3$ per 9-ml. sample.

t (min.)	0	2307	2630	3090	3710	4230	5280	5280	6556
[Picryl chloride]	4·291	3·944	3·896	3·838	3·764	3·682	3·570	3·591	3·443
10^7k_1	—	6·11	6·13	6·02	5·89	6·04	5·80	5·61	5·60

Extrapolation to $t = 0$ gives pseudo-$k_1 = 6{\cdot}35 \times 10^{-7}$, duplicate $k_1 = 6{\cdot}43 \times 10^{-7}$, mean $k_1 = 6{\cdot}39 \times 10^{-7}$. k_2 = pseudo-k_1/(1000/32) = $2{\cdot}00 \times 10^{-4}$ l. sec.$^{-1}$ mole^{-1}.

Analyses of Products.—Reaction (2). Portions (50 ml. each) of 0·1199M-*p*-fluoronitrobenzene and 0·2631M-sodium thiophenoxide in absolute methanol were heated in nitrogen in a sealed ampoule for 22·5 hr. at 49·72°. The tube was chilled in ice, the contents were poured into methanolic hydrogen chloride, and the methanol was distilled off in a stream of nitrogen. The residue was extracted with ether and dilute sodium hydroxide solution; the ethereal layer was shaken four times with dilute sodium hydroxide solution, washed with water, and dried (Na_2SO_4). Distillation of the ether gave a residue which after drying over phosphoric oxide *in vacuo* had m. p. 50·8—53·5° (yield 90%) (Found: C, 62·7; H, 4·1; S, 14·0. Calc. for $C_{12}H_9O_2NS$: C, 62·3; H, 3·9; S, 13·1%). Hence the product is substantially pure 4-nitrodiphenyl sulphide. One recrystallisation from light petroleum raised the m. p. to 54·8—55·2° (Bourgevis and Huber [16] give m. p. 55°).

Oxidation with hydrogen peroxide in glacial acetic acid gave a sulphone, m. p. 144·2—144·7° (Bourgevis and Huber [16] give 143° for 4-nitrodiphenyl sulphone).

Reaction (3). At the temperature used, side reactions produce highly coloured substances. The development of colour was, however, slight over the range of times used for determining rate constants, and since Chapman and Parker [13] found the expected products in an analogous reaction at lower temperatures it is reasonable to assume that the initial consumption of amine is largely concerned in the replacement of fluoride ion. Also, consumption of amine was found to correspond with production of fluoride ion over the range of reaction followed. From a reaction mixture run at 200° for 8 days, 4-nitrodiphenylamine, m. p. 133°, was isolated together with a small quantity of (?) aniline-black.

Reactions (4) *and* (5). In both cases the addition of amine to picryl chloride gave a yellow solution and at the end of the reaction crystals separated from the solution. With aniline, the crystals had m. p. 180·8—181·4° (m. p. of 2 : 4 : 6-trinitrodiphenylamine 179°) [17]; with *m*-nitroaniline, the product had m. p. 212—213° (m. p. of 2 : 4 : 6 : 3′-tetranitrodiphenylamine 213°).[18]

[16] Bourgevis and Huber, *Bull. Soc. chim. France*, 1911, **9**, 947.
[17] Giua and Cherchi, *Gazzetta*, 1919, **49**, II, 157.
[18] Duin and Lennep, *Rev. Trav. chim.*, 1919, **38**, 368.

Reaction (7). Reaction tubes heated to 100° for 5 days were opened, and the product was evaporated to dryness on a water-bath; it had m. p. and mixed m. p. with picric acid 123—123·5°

We acknowledge the benefit of discussion with Professor E. D. Hughes, F.R.S., and Professor M. J. S. Dewar.

UNIVERSITY COLLEGE, IBADAN, NIGERIA. [*Received, June 27th*, 1955.]

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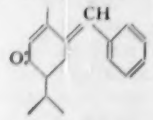
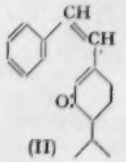
55. *Terpene Compounds. Part VIII.* The Conversion of (±)-Benzylidenepiperitone into 3-iso Propylphenanthrene.*

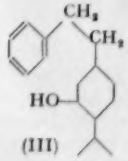
By J. C. BARDHAN and R. N. ADHYA.

(±)-7-Benzyl*iso*menthol (III), on cyclodehydration and then dehydrogenation, furnishes 3-*iso*propylphenanthrene the structure of which is placed beyond doubt by unambiguous syntheses. This proves Earl and Read's view (*J.*, 1926, 2072) as to the structure of (±)-benzylidenepiperitone (II).

READ and his co-workers (*J.*, 1921, 779; 1922, 574; 1936, 1598) found that piperitone readily condenses with benzaldehyde in the presence of sodium ethoxide giving a highly characteristic benzylidene derivative. This was also prepared by Simonsen (*J.*, 1921, 1646; cf. Wallach, *Annalen*, 1913, **397**, 216) who tentatively represented it as (I). On the other hand, Earl and Read (*J.*, 1926, 2072) preferred structure (II), since oxidation with alkaline permanganate gave α-*iso*propylglutaric acid. On reduction (±)-benzylidenepiperitone afforded a saturated alcohol (cf. Read, Smith, and Hughesdon, *J.*, 1924, 135; Read and Smith, *J.*, 1923, 2270) which was accordingly formulated as (±)-7-benzyl*iso*menthol (III), although no further proof was adduced in support of this formulation.

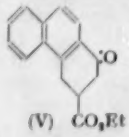

(I)

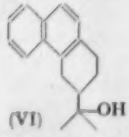

(II)


(III)

It is now found, however, that treatment of the alcohol (III) with phosphoric anhydride gives a "saturated" hydrocarbon, probably (IV), yielding on dehydrogenation with selenium at 310—320° a liquid hydrocarbon, $C_{17}H_{16}$, characterised by a crystalline picrate, styphnate, and trinitrobenzene derivative. On the basis of the structure (II) for (±)-benzylidenepiperitone this should be 3-*iso*propylphenanthrene. This appears not to have been made previously, but we have confirmed this structure by two independent syntheses.

(IV)

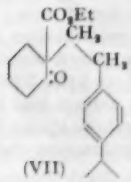

(V) CO_2Et

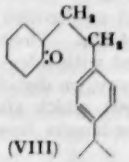

(VI)

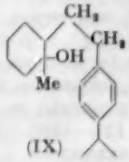
Ethyl 1:2:3:4-tetrahydro-1-oxophenanthrene-3-carboxylate (V), prepared by cyclisation of β-carboxy-γ-1-naphthylbutyric acid according to Bardhan, Nasipuri, and Adhya (*J.*, in the press), was reduced (Clemmensen–Martin) to ethyl 1 : 2 : 3 : 4-tetrahydrophenanthrene-3-carboxylate which was converted in good yield by an excess of methylmagnesium iodide into the alcohol (VI). This was dehydrated with potassium hydrogen sulphate and the product on catalytic hydrogenation followed by dehydrogenation with selenium afforded 3-*iso*propylphenanthrene.

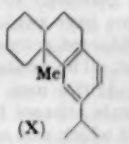
* Part VII, *J.*, 1951, 3195.

Secondly, the Grignard compound from 4-bromocumene (Jacobsen, *Ber.*, 1879, **12**, 430) with ethylene oxide gave 2-*p-iso*propylphenylethyl alcohol. The derived bromide, on condensation with ethyl potassio-2-oxo*cyclo*hexanecarboxylate (cf. Bardhan and Sengupta, *J.*, 1932, 2520), yielded ethyl 2-oxo-1-(2-*p-iso*propylphenylethyl)*cyclo*hexanecarboxylate

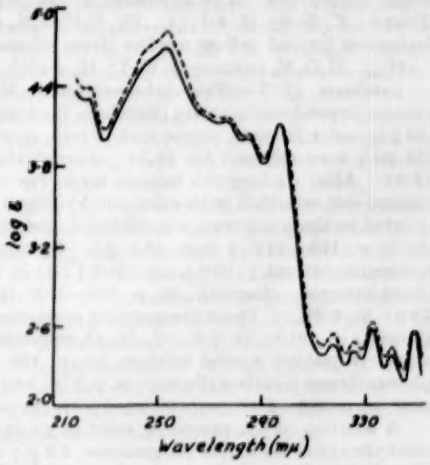

(VII)


(VIII)


(IX)


(X)

(VII). This, on alkaline hydrolysis and decarboxylation (cf. Kon, *J.*, 1933, 1082), gave 2-(2-*p-iso*propylphenylethyl)*cyclo*hexanone (VIII), yielding the alcohol (IX) with methylmagnesium iodide. This was cyclised with phosphoric anhydride to the hydrocarbon (X) which on dehydrogenation with selenium yielded 3-*iso*propylphenanthrene.



Ultraviolet absorption of 3-*iso*propylphenanthrene (——, *synthetic*; – – – – *from piperitone*).

The synthetic hydrocarbon was identified by its b. p. and ultraviolet absorption (see Figure) and as the picrate, styphnate, and trinitrobenzene derivative with the corresponding compound prepared from (±)-benzylidenepiperitone (II).

Cyclodehydration of the substituted *cyclo*hexanol (III), which obviously proceeds through the corresponding olefin (cf. Fieser and Fieser, "Natural Products Related to Phenanthrene," Rheinhold, New York, 3rd edn., 1949, p. 91), is somewhat remarkable since hitherto only the derivatives of 2- and 1-phenethyl*cyclo*hexanol (Bardhan and Sengupta, *loc. cit.*; Bogert, *Science*, 1933, **77**, 289; Perlman, Davidson, and Bogert, *J. Org. Chem.*, 1936, **1**, 288; Cook and Hewett, *J.*, 1933, 1098) have been found to give derivatives of octahydrophenanthrene on cyclodehydration, although, according to Roblin, Davidson, and Bogert (*J. Amer. Chem. Soc.*, 1935, **57**, 151) the analogous cyclisation of 5-phenylpentanol leads to 1-methyltetralin in high yield.

Experimental

(±)-7-*Benzylisomenthol* (III).—(−)-Piperitone, b. p. 98—100°/10 mm. (Messrs. Schimmel and Co.), was converted successively into (±)-benzylidenepiperitone, b. p. 195—197°/5 mm., (±)-7-benzyl*iso*menthone, b. p. 163—164°/3 mm., and (±)-7-benzyl*iso*menthol, b. p. 168—169°/4 mm., as described by Read and his co-workers (*locc. cit.*).

Cyclodehydration and Dehydrogenation (with B. K. GANGULI).—As a result of a large number of experiments the following procedure was adopted which gave reproducible results. The foregoing alcohol (6 g.) was heated under reflux with phosphoric anhydride (12 g.) at 170—180° for 6 hr., then cooled. Powdered ice was added, the solution extracted with ether, and the ethereal solution washed with water, dried, and evaporated. The residual oil was again heated with phosphoric anhydride (12 g.) at 170—180° for 6 hr. at 135—140°/5 mm. for 30 min., and then gradually to 170—180°, whereupon, a liquid (5 g.) distilled which on redistillation over sodium gave a colourless oil (4·6 g.), b. p. 135—140°/5 mm. The hydrocarbon, which could not be obtained sufficiently pure for analysis, was heated with selenium (9·2 g.) at 315—320° for 20 hr. The product (3·8 g.), isolated in the usual way, on distillation over sodium had b. p. 168—170°/4 mm. and gave a picrate, m. p. 95—100°, which after four crystallisations from absolute ethanol had m. p. 127—128°. The mother-liquors from this crystallisation yielded an oil which was not further examined.

3-*iso*Propylphenanthrene.—The pure *hydrocarbon* regenerated from the above picrate, on distillation, finally over sodium, formed a colourless liquid with a faint blue fluorescence and had b. p. 173°/5 mm. (Found : C, 92·6; H, 7·3. $C_{17}H_{16}$ requires C, 92·7; H, 7·3%). The *picrate* prepared from the pure hydrocarbon formed orange yellow needles, m. p. 128—129° (Found : C, 61·3; H, 4·3. $C_{17}H_{16}.C_6H_3O_7N_3$ requires C, 61·5; H, 4·2%), and when pure was of the usual bright appearance. The *styphnate*, bright yellow needles from ethanol, had m. p. 142—143° (Found : C, 58·9; H, 4·1. $C_{17}H_{16}.C_6H_3O_8N_3$ requires C, 59·3; H, 4·1%). The *trinitrobenzene* derivative formed yellow needles (from ethanol), m. p. 138—139° (Found : C, 63·4; H, 4·4. $C_{17}H_{16}.C_6H_3O_6N_3$ requires C, 63·7; H, 4·4%).

Synthesis of 3-*iso*Propylphenanthrene.—*Method* (*a*). Ethyl 1 : 2 : 3 : 4-tetrahydro-1-oxophenanthrene-3-carboxylate (Bardhan, Nasipuri, and Adhya, *loc. cit.*) (10 g.), amalgamated zinc (50 g.), water (10 ml.), acetic acid (2 ml.), concentrated hydrochloric acid (40 ml.), and toluene (25 ml.) were refluxed for 48 hr., concentrated hydrochloric acid (10 ml.) being added every 12 hr. After cooling, the toluene layer was washed with water, dried, and evaporated. The residue was esterified with ethanolic hydrogen chloride (33 ml.; 3%) for 12 hr. The product, isolated in the usual way, was distilled, giving fractions (*a*) b. p. 195—198°/4 mm. (5·8 g.) and (*b*) b. p. 198—210°/4 mm. (3·1 g.). Fraction (*a*), on hydrolysis with ethanolic potassium hydroxide (40 ml.; 10%), afforded 1 : 2 : 3 : 4-*tetrahydrophenanthrene-3-carboxylic acid*, plates (from ethanol; charcoal), m. p. 205—206° (Found : C, 79·8; H, 6·2. $C_{15}H_{14}O_2$ requires C, 79·6; H, 6·2%). The corresponding *ethyl ester* was a pale yellow liquid, b. p. 195—198°/4 mm. (Found : C, 80·3; H, 7·0. $C_{17}H_{18}O_2$ requires C, 80·3; H, 7·1%). Fraction (*b*) on hydrolysis as above yielded a solid mixture (m. p. 196—197°) from which 1 : 2 : 3 : 4-tetrahydro-1-oxophenanthrene-3-carboxylic acid, m. p. 218°, and 1 : 2 : 3 : 4-tetrahydrophenanthrene-3-carboxylic acid, m. p. 205—206°, were isolated with the aid of semicarbazide acetate.

A solution of the preceding ester (5 g.) in dry ether (5 ml.) was gradually introduced into methylmagnesium iodide (magnesium, 2·9 g.; ether, 25 ml.; and methyl iodide, 8·5 ml.), cooled to −10°, and the whole was kept overnight, then refluxed for 5 hr., decomposed with ice and dilute hydrochloric acid, and extracted with ether. The ethereal solution was washed with aqueous sodium hydrogen sulphite and water, dried, and evaporated. The crude alcohol, m. p. 90—92° (6 g.), was boiled with potassium hydroxide (2 g.) in water (5 ml.) and ethanol (30 ml.) for 1 hr. The solution was diluted with water and repeatedly extracted with ether, the ethereal extract washed with water and dried, and the solvent removed. The residual oil (5·1 g.) was then heated with freshly fused and powdered potassium hydrogen sulphate (10·5 g.) at 150° for 1 hr. After cooling, the mixture was mixed with water and extracted with ether, and the ethereal solution washed, dried, and distilled, finally over sodium, giving an almost colourless liquid (4·4 g.), b. p. 189—190°/4 mm. This was dissolved in ethanol (10 ml.) and shaken in an atmosphere of hydrogen with palladous chloride (0·1 g.), gum arabic (0·1 g.), and water (2 ml.) until a little more than 1 mol. of hydrogen had been absorbed. The product was worked up in the usual manner and distilled; almost the whole amount (4·0 g.) boiled constantly at 173°/4 mm. This was heated with selenium (8 g.) at 315—320° for 24 hr. 3-*iso*Propylphenanthrene (3·6 g.), thus obtained, readily yielded a picrate as orange yellow needles, m. p. 131—132° (Found : C, 61·3; H, 4·3%), a styphnate, yellow needles, m. p. 142—143° (Found : C, 58·9; H, 4·1%), and a trinitrobenzene derivative, yellow needles, m. p. 138—139° (Found : C, 63·4; H, 4·4%). The pure hydrocarbon regenerated from its picrate formed a colourless oil, b. p. 173°/5 mm., which exhibited a weak blue fluorescence (Found : C, 92·6; H, 7·3%).

Method (*b*). A solution of ethylene oxide (25 g.) in dry ether (50 ml.) was gradually added to an ice-cold solution of the Grignard reagent prepared from magnesium (5·4 g.), 4-bromocumene

(Jacobsen, *loc. cit.*) (44·7 g.), and dry ether (70 ml.). The product which set to a semisolid mass was set aside overnight in the cold, excess of ether distilled off at 60°, and the residue decomposed by ice and dilute hydrochloric acid. 2-p-iso*Propylphenylethyl alcohol*, isolated with ether, was a colourless oil (18·5 g.), b. p. 136—140°/13 mm. (Found : C, 80·3; H, 9·7. $C_{11}H_{16}O$ requires C, 80·5; H, 9·7%). This alcohol (18·2 g.) was added dropwise to phosphorus tribromide (5·2 ml.), the mixture heated on the steam-bath for 1·5 hr. and then poured into ice, and the oil collected in ether. 2-p-iso*Propylphenylethyl bromide* (21 g.) had b. p. 127—130°/13 mm. (Found : Br, 34·9. $C_{11}H_{15}Br$ requires Br, 35·2%). Finely divided potassium (6·8 g.) was kept under xylene (100 ml.), and ethyl 2-oxo*cyclo*hexanecarboxylate (Kotz and Michels, *Annalen*, 1906, **350**, 204) (29·7 g.) gradually introduced with cooling and occasional swirling. The clear solution which resulted was mixed with 2-*p-iso*propylphenylethyl bromide (39·7 g.), and the whole heated at 152—157° for 40 hr. After cooling, water was added and the xylene layer separated, dried, and distilled. *Ethyl* 2-*oxo*-1-(2-p-iso*propylphenylethyl*)cyclo*hexanecarboxylate* (VII) was a pale yellow oil (32·3 g.), b. p. 191—193°/4 mm. (Found : C, 75·7; H, 8·9. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·8%). It gave no colour with ethanolic ferric chloride. This keto-ester (16 g.) was boiled with potassium hydroxide (10 g.), water (10 ml.), and ethanol (18 ml.) for 1 hr. After removal of the excess of ethanol, the solution was acidified and extracted with ether, and the ethereal solution dried (Na_2SO_4) and evaporated. The residual oily acid (14·6 g.) was heated with barium hydroxide (2 g.) at 315° until no more liquid distilled over. 2-(2-p-iso*Propylphenylethyl*)cyclo*hexanone* (VIII) (6·7 g.), recovered from the aqueous distillate, formed an almost colourless liquid, b. p. 157—160°/4 mm. (Found : C, 83·4; H, 9·9. $C_{17}H_{24}O$ requires C, 83·6; H, 9·8%). The *semicarbazone* crystallised from aqueous ethanol in prisms, m. p. 132—133° (Found : C, 71·3; H, 8·8. $C_{18}H_{27}ON_3$ requires C, 71·7; H, 8·9%). The above ketone (6·2 g.) in dry ether (5 ml.) was allowed to react with methylmagnesium iodide (magnesium, 0·8 g.; methyl iodide, 2·3 ml.; dry ether, 20 ml.) in the usual way, and finally heated for 1 hr. 1-*Methyl*-2-(2-p-iso*propylphenylethyl*)cyclo*hexanol* (IX) (6·2 g.) was thus obtained as a viscous oil, b. p. 160°/3 mm. (Found : C, 82·9; H, 10·6. $C_{18}H_{28}O$ requires C, 83·1; H, 10·8%). The alcohol (5·8 g.) was heated with phosphoric anhydride (12·4 g.) under the standard conditions (cf. Bardhan and Sengupta, *loc. cit.*). The product was extracted with light petroleum (b. p. 60—80°), and the petroleum solution washed with 85% sulphuric acid and water, dried, and distilled, finally over sodium, giving 1 : 2 : 3 : 4 : 9 : 10 : 13 : 14-*octahydro*-13-*methyl*-3-iso*propylphenanthrene* (X) (4·3 g.) as a colourless liquid having a characteristic bluish green fluorescence, b. p. 136—137°/4 mm. (Found : C, 89·1; H, 10·6. $C_{18}H_{26}$ requires C, 89·2; H, 10·7%). This (4·0 g.) was heated with selenium (8 g.) at 320—325° for 26 hr. and the product worked up in the usual way. On distillation over sodium, 3-*iso*propylphenanthrene (2·6 g.) had b. p. 165—170°/3 mm., and showed no tendency to solidify. The picrate, after four crystallisations from absolute ethanol, had m. p. 128—129° (Found : C, 61·3; H, 4·3%), indistinguishable from the corresponding derivative prepared from (±)-7-benzyl*iso*menthol as described above.

The ultra-violet absorption spectra were measured in purified ethanol with a Beckman spectrophotometer, model DU, and we express our indebtedness to Dr. (Miss) K. Rohatgi for much valuable assistance.

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56. *The Reversibility of the Adsorption of Catalyst Poisons. Part IV.* Revival of Poisoned Catalysts by Gas-phase Desorption.*

By E. B. Maxted and M. Josephs.

The revival of platinum hydrogenation catalysts, previously poisoned by thiophen or diethyl sulphide, by a method involving the desorption of the poison into the gas phase, has been studied as an alternative to the liquid-phase desorption method described in earlier papers of this series. This desorption has been carried out in three ways, namely, by simple evacuation, by circulating an inert gas through the poisoned catalyst, and by circulating gaseous ethylene all at room temperature. These procedures are gas-phase analogues of liquid-phase revivals by direct desorption into a solvent and by displacing the poison by the competitive adsorption of a second substrate.

It has been shown in an earlier paper of this series [1] that platinum or nickel hydrogenation catalysts which have been inactivated by various poisons, including dimethyl sulphide, thiophen, or toxic metallic ions, can be easily revived by a liquid-phase desorption or desorptive displacement method applied at room temperature and involving, respectively, the simple washing of the poisoned catalyst with a suitable solvent alone or with a solvent containing a displacing agent such as an unsaturated substance. In view of this rather unexpected reversibility of the adsorption of typical strong poisons even at room temperature, we have now studied the degree to which catalysts poisoned by volatile sulphur compounds can be revived by a similar desorption of the poison into the gas phase. In preliminary work [2] the activity of poisoned platinum catalysts was thus considerably improved but complete revival was not reached.

In the present, more systematic work, a complete revival of platinum catalysts poisoned either by thiophen or by diethyl sulphide was obtained at room temperature by three methods involving, severally, (i) the direct removal of the poison by evacuation, (ii) its removal by circulating an inert gas through the catalyst, and (iii) the desorptive displacement of the poison from the poisoned surface by circulating ethylene. Method (ii) is closely related to method (i), since if, as is known from other work, the poison–catalyst adsorption complex has a significant dissociation pressure, poison should be removed continuously from the poisoned catalyst either by direct evacuation or by continuously changing an inert atmosphere above the catalyst surface. Method (iii) corresponds to the liquid-phase procedure involving the displacement of the relatively small amount of adsorbed poison from the surface by the mass action of a relatively large concentration of a less strongly adsorbed species, which process was, in the liquid-phase work, carried out by washing the poisoned catalyst with a solution of an ethylenic compound.

Experimental

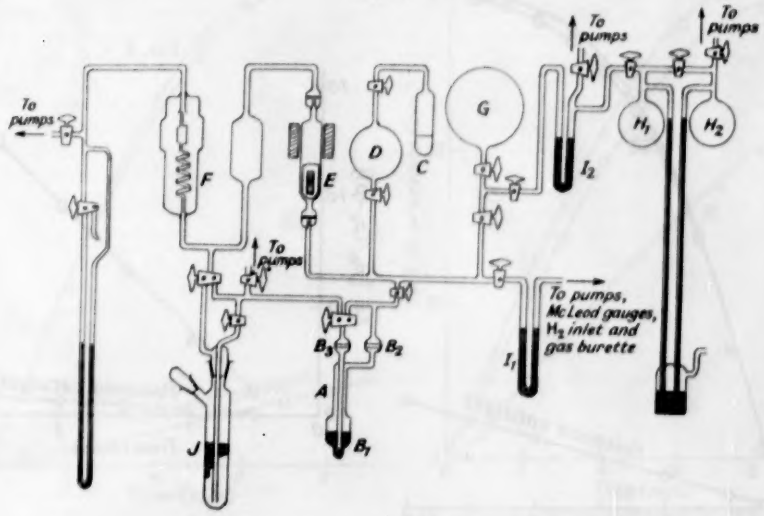
Apparatus.—This (Fig. 1) consists of a catalyst chamber, *A*, containing 12·5 g. of platinum black which, in the course of the work, was alternately poisoned and revived. B_1, B_2, and B_3 are porous sintered-glass discs, as a safety measure to retain the platinum in case of an accidental sudden change of pressure in the rest of the apparatus. The poison was contained as a liquid in a reservoir, *C*, which served as a source for the periodical filling of a poison-vapour reservoir, *D*, from which known amounts of poison vapour could be delivered to the remainder of the apparatus and eventually to the catalyst. Since circulation was required both for the determination of the catalytic activity of the platinum by the gas-phase hydrogenation of ethylene and for methods (ii) and (iii) of revival, an all-glass, magnetically operated circulating pump, *E*, was provided, with appropriate circuits for the circulation either of an ethylene–hydrogen mixture or, alternatively, either of nitrogen or of ethylene alone. The pressure in the pertinent section of the apparatus, by means of which either the adsorption of the poison vapour on the

* Part III, *J.*, 1954, 2778.

[1] Maxted and Ball, *J.*, 1952, 4284 (Part I).
[2] G. T. Ball, Thesis, Bristol, 1953, pp. 126 *et seq.*

catalyst during a poisoning operation or the course of the hydrogenation during an activity determination was followed, could be read accurately on a Bourdon-type glass spiral gauge, *F*, from the mirror of which an optical image of the cross-wires of a lamp could be projected on to a distant scale. A storage bulb, for gaseous ethylene, *G*, was fed as required from liquid-ethylene reservoirs, H_1 and H_2, these liquid storage vessels being kept at −180° in liquid air, which was removed temporarily and with due caution when *G* was to be filled. The apparatus could be evacuated by a normal high-vacuum train; but a special feature of the apparatus was a provision for pumping off adsorbed poison from the catalyst by connection to a "cold-limb," *J*, which contained Fenske helices and could be immersed in liquid air. In this way, a very low poison pressure could, in the absence of other gases, be induced in the apparatus; and any poison pumped off from the platinum was condensed in a state having a very low pressure in the cooled limb. It was found that this acted as a very efficient pump: and it was, in all later stages of the work, used in preference to evacuation of the poisoned catalyst by means of the available high-vacuum system, particularly since the latter system had to be

FIG. 1.



protected from contamination by poison. The apparatus included some mercury-filled gauges and safety valves; but the access of mercury vapour from these and from the mercury diffusion pump to the platinum was prevented by traps, I_1 and I_2, containing gold leaf and cooled in liquid air. The volumes of all pertinent parts of the apparatus were determined by calibration.

General Procedure.—In the cycle represented by poisoning followed by subsequent revival, the activity of the catalyst was measured at at least three stages, namely, in its original, poisoned, and revived states. In poisoning, a known amount of diethyl sulphide or thiophen vapour was admitted from the bulb, *D*, and the adsorption read off on the spiral pressure gauge. In the experiments in which the revival was carried out either by cold-limb pumping or by the circulation of an inert gas, the amount of poison adsorbed by the catalyst, and subsequently removed during the revival and condensed at −180° in the cold limb, *J*, could be checked by removing the liquid-air bath from this limb and allowing the condensed poison to evaporate into the spiral pressure gauge; but, at the time of the revival by ethylene circulation, this checking method had not yet been developed.

Activity Determinations.—In these, an equimolecular ethylene–hydrogen mixture, initially at approximately atmospheric pressure, was circulated through the catalyst by means of the magnetic pump, the fall in the pressure with the time as the hydrogenation proceeded being followed by reading the movement of the beam of light from the spiral pressure gauge.

The ethylene-hydrogenation velocity, at 0°, which was used as a measure of the activity

of the catalyst at any given stage, is known [3] to vary approximately directly with the partial pressure of the hydrogen, at any rate up to not too advanced stages of the hydrogenation, after which the ethylene partial pressure begins also to exercise some control of the rate, though far less at 0° than at higher temperatures.[4] Consequently, during early stages of the hydrogenation at constant volume, in which the pressure falls continuously as a result of the process, the change in pressure with the time will follow a course which in its integrated form becomes $kt = \log\{p_0/(p_0 - p)\}$, in which p_0 is the initial partial pressure of the hydrogen, p the fall in the pressure of the system after time, t, and k is a reaction velocity constant. This relation should give a linear plot of $\log\{p_0/(p_0 - p)\}$ against the time, from the slope of which the value of k can conveniently be read off.

Revival Procedure.—The removal of the poison from the catalyst by simple evacuation at room temperature, by either of the methods described, needs no special description.

In revivals by nitrogen or ethylene circulation, the cold trap was used, not as a pump but

FIG. 2. *Revival by simple evacuation.*

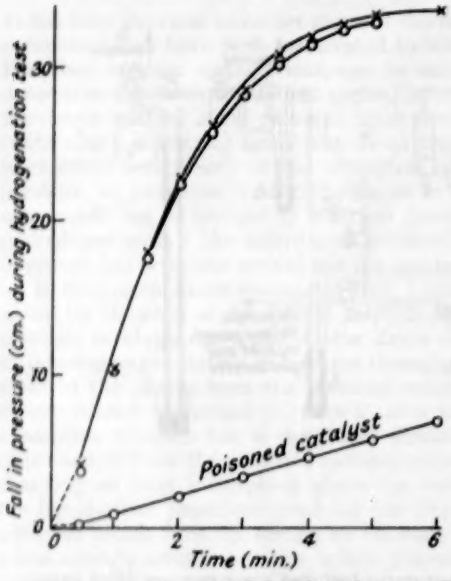
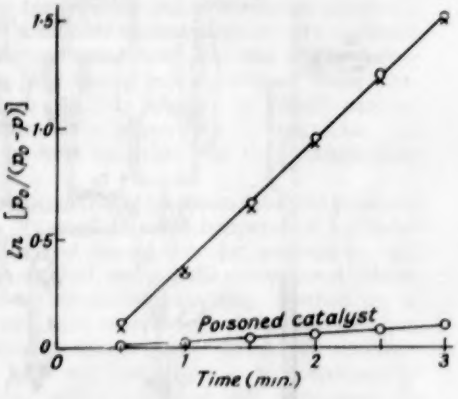


FIG. 3.



○ Original catalyst. × Poisoned catalyst after revival.

as a means of freeing the circulating gas from entrained poison carried over from the catalyst, in such a way that clean gas was continuously re-passed through the platinum, the trap being placed in the gas circuit on the exit side of the catalyst chamber. The trap was maintained at −180° during the circulation of nitrogen and at −80° during ethylene circulation.

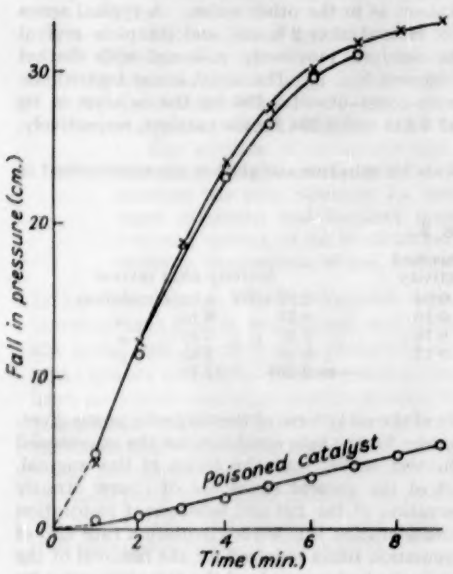
Typical Revival Cycles.—Revival by the circulation of ethylene was studied first, by reason of the previous successful revivals of poisoned catalysts in the liquid phase by desorptive displacement of poisons by treatment with a dissolved unsaturated substance. This was followed by a series involving revivals by simple evacuation and by a single set of runs in which an inert gas was circulated through the poisoned catalyst. During the work, the general accuracy of the measurements was progressively increased, mainly by increasing the efficiency and constancy of operation of the magnetic circulating pump and also by the introduction of the analytical method already described for checking the amount of poison on the catalyst. It is considered that conditions in the simple evacuation series were more precise than in the ethylene series, the revival by nitrogen circulation occupying an intermediate position. Accordingly, in the

[3] Beeck, Smith, and Wheeler, *Proc. Roy. Soc.*, 1940, *A*, **177**, 62.
[4] Rideal, *J.*, 1922, **121**, 309; Pease, *J. Amer. Chem. Soc.*, 1923, **45**, 1196.

following account, the various revival types have been arranged in the above order of their probable precision, in place of the order in which the work was carried out.

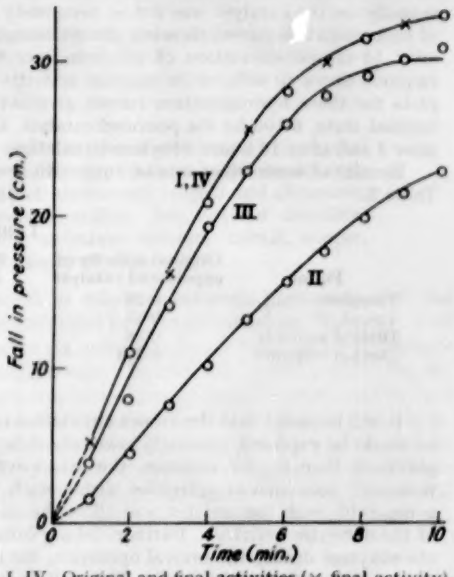
(i) *Revival of the catalyst by simple evacuation.* A representative revival by this method, using the cold limb as a vacuum pump, is summarised in Fig. 2, which contains the hydrogenation curves given by the platinum catalyst, first in its original unpoisoned state, secondly after being poisoned by $1{\cdot}5 \times 10^{-4}$ mole of diethyl sulphide down to about 7% of its unpoisoned activity, and, finally, after having been revived by evacuation for 13 hr. at room temperature. In each of the hydrogenation tests, a period of about 0·5 min., from the starting of the magnetic pump circulating the mixture of ethylene and hydrogen, was required before steady hydrogenation conditions were established; but the curves for the original and for the revived platinum were identical within the experimental limits of accuracy and showed a complete

FIG. 4. *Revival by circulation of inert gas.*



○ Original catalyst.
× Poisoned catalyst after revival.

FIG. 5. *Revival by circulation of ethylene.*



I, IV. Original and final activities (× final activity).
II. Poisoned catalyst.
III. Activity after 2 hours' revival.

recovery to the original activity. Good linear plots (Fig. 3) of $\log\{p_0/(p_0 - p)\}$ against the time were given over the period from ½—3 min., by which time about 80% of the total hydrogenation had taken place. From the slope of these lines, the velocity constants representing the relative activity of the platinum in its three states can be calculated to be 0·56, 0·04, and 0·56, respectively, for the original, for the poisoned, and for the revived catalyst.

TABLE 1.

Amount of poison (10^{-4} mole)		Activity (k) of catalyst		
Applied	Recovered in cold trap	Before poisoning	After poisoning	After revival
1·7	1·9	0·57	0·039	0·51 after 18 min. evacuation
				0·52 ,, 36 ,, ,,
				0·58 ,, 12 hr. ,,
1·9	1·7	0·57	0·038	0·57 after 13 hr. evacuation

Two other examples of revival by evacuation, in each case by cold-limb pumping, are summarised in Table 1. The poison was diethyl sulphide.

It will be seen that complete revival was obtained in each case after evacuation for 12—13 hr.

(ii) *Revival by circulation of inert gas.*—A set of hydrogenation curves for a revival by treatment with an inert gas is given in Fig. 4, the catalyst being first poisoned by 2×10^{-4} mole of ethyl sulphide and then revived at room temperature by circulation of nitrogen for 28 hr. in a closed circuit in which the gas passed continuously through the poisoned catalyst, then through the cold trap at $-180°$ to remove entrained poison from the gas stream, and again through the platinum. These curves give good linear plots of $\log\{p_0/(p_0 - p)\}$ against time from 1 to 5 min. The corresponding catalytic activity constants, k, obtained from these linear plots, are 0·30 for the unpoisoned catalyst, and 0·024 and 0·36, respectively, for the catalyst in its poisoned and in its revived state, the apparent increase beyond its original activity in this case being probably due to a variation in the circulating efficiency of the magnetic pump in the last activity determination.

(iii) *Revival by ethylene circulation.* In this series both diethyl sulphide and thiophen were used as poisons and, in general, the catalyst was not so heavily poisoned as in the later work already described: further, in the absence of the checking method, the amount of poison actually on the catalyst was not so accurately known as in the other series. A typical series of hydrogenation curves showing almost complete revival after 2 hours' and complete revival after 16 hours' circulation of ethylene over the catalyst, previously poisoned with diethyl sulphide down to 40% of its original activity is shown Fig. 5. The usual linear logarithmic plots for these hydrogenation curves give activity constants of 0·256 for the catalyst in its original state, 0·103 for the poisoned catalyst, and 0·215 and 0·254 for the catalyst, respectively, after 2 and after 16 hours' ethylene circulation.

Results of some other sets of runs with revivals by ethylene circulation are summarised in Table 2.

TABLE 2.

Poison	Original activity of unpoisoned catalyst	Poisoned activity	Activity after revival
Thiophen	0·22	0·08	0·22 after 4 hr. circulation
Thiophen	0·23	0·10	0·23 ,, 6 hr. ,,
Diethyl sulphide...	0·26	0·18	0·30 ,, 2 hr. ,,
Diethyl sulphide...	0·254	0·12	0·19 ,, 2 hr. ,,
			⟶ 0·256 ,, 13 hr. ,,

It will be noted that the known circulation rate of the early form of the magnetic pump gives, as would be expected, generally lower absolute values for the rate constants for the unpoisoned platinum than in, for instance, the direct-evacuation series; but the ratios of the original, poisoned, and revived activities within each set of the present series are of course strictly comparable with one another and allow the observation of the fall and subsequent restoration of the catalytic activity. Further, taking into consideration this lower circulation rate also of the ethylene during the revival operation, the circulation times required for the removal of the poison are often notably short. This will be seen in the first example of the thiophen series by the complete revival after 4 hours' circulation, and indeed in the diethyl sulphide series by a complete revival after 2 hr. only. In one case, the revival was slower, but in this no intermediate measurements of the activity between 2 and 13 hr. were made, and the latter time may have been longer than was necessary for the restoration of the activity. It would be expected, from experience in liquid-phase revivals, that ethylene circulation would be, under similar conditions, more effective than the circulation of an inert gas.

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57. *Ion-exchange Studies of Phosphates. Part I. Ion-exchange Sorption and* pH*-Titration Methods for Detection of Complex Formation*

By A. Holroyd and J. E. Salmon.

The sorption of metal and phosphate from solutions of the metal phosphates in phosphoric acid by the phosphate form of an anion-exchange material has provided evidence of complex formation between phosphate ions and the tervalent ions of aluminium, chromium (aged solutions), iron, and indium, and also bismuth (solutions of bismuth phosphate in hydrochloric acid). With the bivalent metals a slight sorption of metal by the anion-exchange material was found for manganese, but none for barium, calcium, cadmium, cobalt, copper, mercury, magnesium, nickel, lead, strontium or zinc.

The results of pH titrations of solutions of the metal sulphates with phosphoric acid have also indicated complex formation with tervalent aluminium, chromium (aged solutions), iron, and indium, but not (to any significant extent) with bivalent cadmium, cobalt, copper, magnesium, manganese, nickel, or zinc.

The sorption of phosphate with the metal from solutions of the metal phosphate in phosphoric acid by the hydrogen form of a cation-exchange material has been observed for tervalent aluminium (slight) and chromium (aged solutions) and bivalent manganese (slight), but not for tervalent iron and indium, or for bivalent barium, cadmium, calcium, cobalt, copper, mercury, magnesium, nickel, lead, strontium, or zinc.

It has been shown [1-3] that complex formation in solution between phosphate and the tervalent ions of iron, aluminium, and chromium could be demonstrated by the sorption of the metal ions together with phosphate ions on an anion-exchange resin or of phosphate ions together with metal ions on a cation-exchange resin. In addition, Everest and Salmon [4] have used anion exchange studies to show the formation of complexes between quadrivalent germanium and phosphate. In the present work the species sorbed by cation- and anion-exchange materials respectively from phosphoric acid solutions of some bi- and ter-valent metal phosphates have been examined. The results, which show complex formation to be much more important with tervalent than with bivalent metals, have been checked by the pH-titration method which had already proved useful in the study of aluminium and iron phosphate complex compounds.[2, 5, 6]

Experimental

Ion-exchange Experiments.—Solutions were prepared by saturating portions (*ca.* 150 ml.) of 1M-phosphoric acid with various metal phosphates. Each solution was then diluted with 1/20th of its own volume of 1M-phosphoric acid so that the possibility that metal phosphate might crystallize on the resin would be avoided. With antimony, bismuth, and stannous phosphates so little of the phosphate dissolved in the phosphoric acid solution used that the metal ions could not be detected readily by standad qualitative tests. Ion-exchange experiments were not carried out with these phosphates, except that of bismuth which was dissolved in 0·5N-hydrochloric acid.

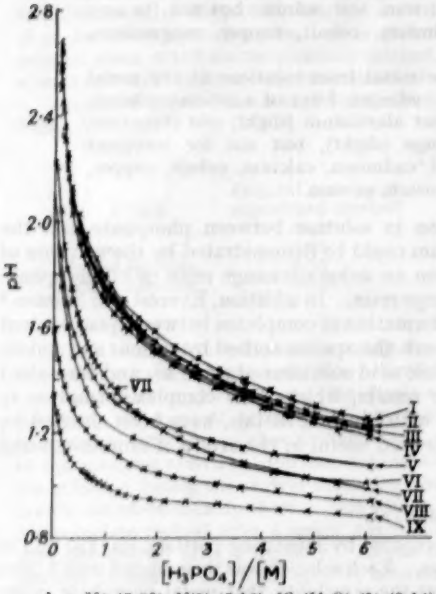
To each of two 50 ml. portions of each of the final solutions were added 0·500 g. of Zeo Karb 225-H and 1·000 g. of I.R.A.-400-PO_4 respectively. The solutions were kept in contact with the resin in a stoppered flask for at least a week, with frequent shaking. The resin was filtered off into a small column and washed with water, rapidly at first to remove the bulk of the adhering solution, and then until the washings were free from metal or phosphate. The species sorbed on the resin were eluted with nitric or, in a few cases, hydrochloric acid (300 ml.; 3N). The

[1] Salmon, *J.*, 1952, 2316.
[2] *Idem*, *J.*, 1953, 2644.
[3] Jameson and Salmon, *J.*, 1954, 28, 4013; 1955, 360.
[4] Everest and Salmon, *J.*, 1955, 1444.
[5] Bjerrum and Dahm, *Z. phys. Chem., Bodenstein Festband*, 1931, 627.
[6] Salmon and Wall, unpublished work.

eluate was evaporated to small bulk and portions tested for metal ions and phosphate by standard procedures.

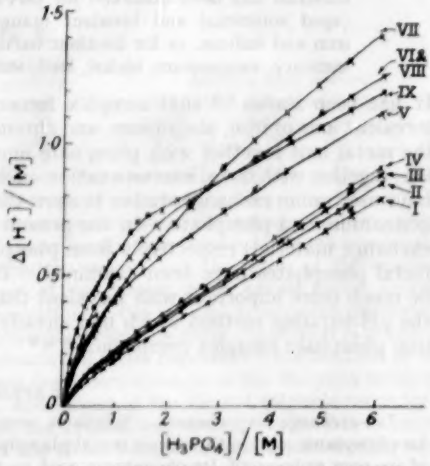
pH-*Titration Experiments.*—Phosphoric acid (approx. 1·5M) was added to a metal sulphate solution (25 ml.; 0·1M in metal ion) in small portions from a burette. The pH of the solution was measured initially and after each addition of phosphoric acid with a glass electrode–saturated calomel electrode system and commercial pH meter. The pH values which are given in Fig. 1 have been converted into hydrogen-ion concentrations and the increase in hydrogen-ion concentration ($\Delta[H^+]$) over that of the original solution derived, and in Fig. 2 the values of $\Delta[H^+]/[M]$ have been plotted against the corresponding values of $[H_3PO_4]/[M]$, where [M] = total metal-ion concentration. Allowance was made in the calculation for the progressive dilution of the solution on addition of the phosphoric acid. The metal sulphates were chosen for these experiments because a wide range of pure sulphate was available and also because a comparison with the pH-titrations already carried out with the chlorides of iron [2] and aluminium [6] could thus be made.

FIG. 1. pH-*Titrations of metal sulphate solutions* (0·1M *in metal*) *with phosphoric acid* (1·5M).



I = K^+ (5·86), Ni^{2+} (5·18), $[Cr(H_2O)_6]^{3+}$ (3·14).
II = Mg^{2+} (5·41), Zn^{2+} (5·40), Co^{2+} (3·90).
III = Mn^{2+} (4·98).
IV = Cd^{2+} (5·27), Cu^{2+} (4·18).
V = Cr^{3+} (2·23) [aged 9 weeks at 25°].

FIG. 2. *Increase in hydrogen-ion concentration during* pH *titration.*



VI = Cr^{3+} (2·03) [aged 24 weeks at 40°].
VII = Al^{3+} (3·13).
VIII = In^{3+} (1·59).
IX = Fe^{3+} (1·34).

The figures in parentheses refer to the pH values of the sulphate solutions used (no phosphate added).

In the case of the chromic sulphate solutions the results obtained depended on whether the pH-titration was carried out rapidly (completed in 1 hr.) or slowly (solutions aged before pH measurements). In order to study the effect of ageing, various known amounts of phosphoric acid were added to 100 or 150 ml. portions of chrome alum solution (0·1M in Cr) and the mixtures kept in sealed containers at 25° or 40°. After various intervals of time samples were withdrawn and cooled to *ca.* 20° before pH measurements were made.

Results.—Anion-exchange experiments. Sorption of the metal with the phosphate on the anion exchange material was observed for tervalent aluminium, bismuth (from 0·5N-hydrochloric acid solution), chromium (aged solutions), indium, and iron, and for bivalent manganese (slight trace only). No sorption of metal was found for bivalent barium, cadmium, calcium, cobalt, copper, lead, magnesium, mercury, nickel, strontium, and zinc.

Cation-exchange experiments. Sorption of phosphate on the cation-exchange material was observed for aluminium, chromium (aged solutions), and bivalent manganese (very slight trace), but not for tervalent bismuth (no bismuth sorbed either from 0·5N-hydrochloric acid), indium, or iron, or for bivalent barium, cadmium, calcium, cobalt, copper, lead, magnesium, mercury, nickel, strontium or zinc.

pH-*Titrations.* The results are shown in Figs. 1 and 2. The curves are very nearly identical with those for potassium sulphate in the cases of bivalent cadmium, cobalt, copper, magnesium, manganese, nickel, and zinc, and tervalent chromium sulphates {$[Cr(H_2O)_6]^{3+}$, not aged}. It may be deduced that in these cases the increase in hydrogen-ion concentration of the solutions is due solely to the hydrogen ions of the phosphoric acid added and that there is no complex formation. Support for this conclusion is provided by the fact that this group includes the ion $[Cr(H_2O)_6]^{3+}$ (solutions not aged) for which no interaction with phosphate occurs during the time taken to carry out a pH-titration (at room temperature).

The rapid increase in hydrogen-ion concentration in the course of the titration of the sulphates of aluminium, chromium (solutions aged at 25° or 40°), indium, and iron, on the other hand, indicates the occurrence of reactions of a type previously reported,[8] namely,

$$Fe^{3+} + H_3PO_4 \rightleftharpoons FeHPO_4^+ + 2H^+$$

and hence of complex formation.

The increase in hydrogen-ion concentration is less in the titration of iron and aluminium sulphates than it is in the titration of the corresponding chlorides.[2,6] This may arise because the chloro-complexes of these metals are more labile than the sulphato-complexes and the chloro-groups are more easily displaced by phosphate than are the sulphate groups.

In the case of chromium, ageing of the sulphate solution alone (no phosphate added) caused an increase in hydrogen-ion concentration (pH fall from 3·14 to 2·06—2·48 depending on time and temperature of ageing), but the increase was always greater with phosphate present and also dependent on the phosphoric acid concentration (Fig. 2), thus showing the formation of phosphato-complexes to be occurring. Nevertheless, the reactions are slow and, whilst equilibrium was reached after three weeks at 40°, it was probably still not reached after 9 weeks at 25° as the pH values recorded then were markedly lower than those obtained after five weeks.

Discussion

The correlation between the results of the anion-exchange and pH-titration studies is satisfactory. According to both methods complex formation occurs with the tervalent metals, but not with the bivalent ones to any significant extent. The only exception, according to the anion-(and also cation-)exchange experiments, is bivalent manganese. The sorption of manganese on the anion-exchange material was only slight, but was consistently observed when the experiment was repeated with both commercial and pure manganese phosphate (the latter prepared by Salmon and Terrey's [7] method). The differences between the pH-titration curves for the bivalent metals (Fig. 1) are barely greater than the experimental error, but may indicate a very slight degree of complex formation for cadmium and copper, and possibly manganese. Nevertheless, it is not considered wise to assign stabilities (even qualitatively) to the bivalent metal complexes or yet to compare them with those predicted by Irving and Williams.[8]

The cation-exchange experiments with the phosphate solutions provide evidence of complex formation for aluminium, chromium, and possibly manganese(II) only, but not for iron or indium for both of which complex formation is indicated by the other two methods. The results obtained are in accord with those of Jameson and Salmon for aluminium, chromium, and iron.[3] Only in the case of chromium is an appreciable amount of phosphate sorbed by the cation exchanger from pure phosphate solution, yet it has been found [2,6] that the cationic complexes of aluminium and iron are sorbed by the exchanger when present, as in solutions containing the anion of a strong acid (*e.g.*, in $AlCl_3$–NaH_2PO_4 or $FeCl_3$–H_3PO_4 solutions). Thus with the tervalent metals indium, iron, and (to a lesser extent) aluminium the equilibria :

$$M^{3+} \rightleftharpoons [M(HPO_4)]^+ \rightleftharpoons [M(HPO_4)_2]^- \rightleftharpoons [M(HPO_4)_3]^{3-}$$

[7] Salmon and Terrey, *J.*, 1950, **2813**.
[8] Irving and Williams, *J.*, 1953, **3192**.

must lie well to the right in the pure phosphate solutions. Although the concentration of HPO_4^{2-} ions must be low in the solutions of phosphoric acid used, the presence of anionic complexes in them shows that the phosphate group must act as a chelate group in the complexes. Otherwise if equilibria of the type:

$$M^{3+} \rightleftharpoons [M(H_2PO_4)]^{2+} \rightleftharpoons [M(H_2PO_4)_2]^{+} \rightleftharpoons [M(H_2PO_4)_3]^{0}$$
$$\rightleftharpoons [M(H_2PO_4)_4]^{-} \rightleftharpoons [M(H_2PO_4)_5]^{2-} \text{ etc.}$$

were involved, four or more phosphato-groups would have to be co-ordinated to the central atom. Complexes with so many ligand groups, which would be expected to show a greater tendency to dissociate into those containing fewer attached groups (including cationic ones) except at high phosphate-ion concentrations, have not been observed in the quantitative ion-exchange studies carried out so far.[2, 3, 6] Thus, although chelation must involve some steric strain in forming the four-membered ring, the increased stability arising from it must more than compensate for this.

The sorption of bismuth by the anion-exchange material from the solution of bismuth phosphate in hydrochloric acid is in accord with Jensen's evidence [9] for the existence of an anionic chloro-phosphato-bismuth complex.

It is possible that complexes of marked stability only would be detected by the methods used—thus, we have not observed the interaction between calcium and phosphate ions reported by other workers.[10] Nevertheless, the results indicate clearly a difference in behaviour between the bivalent and tervalent metals which is certainly greater than might have been expected. This difference may be exploited in ion-exchange chromatography with phosphoric acid as eluant and a preliminary account has already been given of its application in the separation of tervalent from bivalent metals.[11]

The authors thank Mr. J. G. L. Wall for carrying out the pH titration with aluminium sulphate solution.

BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, August 23rd*, 1955.]

[9] Jensen, *Z. anorg. Chem.*, 1934, **219**, 238.
[10] Davies and Hoyle, *J.*, 1953, 4134; Gosselin and Coghlan, *Arch. Biochem. Biophys.*, 1953, **45**, 301.
[11] Genge, Holroyd, Salmon, and Wall, *Chem. and Ind.*, 1955, 357.

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58. *The Localization Theory of Organic Reactions. Part III.* Radical Substitution in Pyridine.*

By R. D. BROWN.

Kooyman and Farenhorst's data (*Trans. Faraday Soc.*, 1953, **49**, 58) for the rates of attack of polycyclic aromatic hydrocarbons by radicals have been used to determine the quantitative relation between rates of attack and the corresponding molecular-orbital localization energies, A_r. This relation has been used in conjunction with Hey and Williams's results (*Discuss. Faraday Soc.*, 1953, **14**, 216) for the partial rate factors for phenylation of pyridine to yield a unique set of molecular-orbital parameters for nitrogen, *viz.*: $\alpha_N = \alpha_C + 0{\cdot}5\beta$, $\beta_{CN} = \beta_{CC} = \beta$.

Rates of attack at the pyridine positions relative to a benzene position calculated from atom-localization energies, A_r, by using these parameters, agree within 10% with experimental rates.

The molecular-orbital theory of chemical reactivity in conjugated compounds has been used successfully to interpret and predict chemical properties of hydrocarbons. For heterocyclic compounds the theory has been somewhat limited because the numerical values of the

* Part II, *J.*, 1952, 2229.

parameters applying to heteroatoms are not at all well known. Thus in the molecular-orbital treatment of nitrogen heterocycles it is customary to use two parameters, h and k, defined by:

$$\alpha_N = \alpha_C + h\beta; \quad \beta_{CN} = k\beta$$

in which α_C is the coulomb integral of carbon and β the standard resonance integral of a carbon–carbon bond. Recent work on homolytic substitution in aromatic compounds has provided valuable evidence for evaluating the theoretical parameters. Thus if Hey and Williams's results (*Discuss. Faraday Soc.*, 1953, **14**, 216) on the relative yields of isomers in the phenylation of pyridine are assumed to be a measure of the relative rates of radical substitution at positions 2, 3, and 4 the values of the parameters h and k which yield localization energies in best agreement with experiment can be determined, as shown below.

It is not satisfactory to discuss the reactivities of heterocycles (or, for that matter, benzene derivatives) towards radicals in terms of free valencies because the theoretical justification in terms of approximate activation energies cannot then be made (Brown, *J. Chim. phys.*, 1953, **50**, 109; further results to be published; cf. Burkitt, Coulson, and Longuet-Higgins, *Trans. Faraday Soc.*, 1951, **47**, 553). One must therefore use the localization theory, interpreting the reactivities in terms of the appropriate atom-localization energies, A_r (Brown, *Quart. Rev.*, 1952, **6**, 63).

The localization energies represent the part of the activation energy arising from π-electron redistributions. In the localization theory we assume that it is only this contribution to the activation energy which varies from one aromatic position to another; this assumption has been shown to be extraordinarily good for another type of homolytic reaction (Brown, *J.*, 1951, 1955; *Quart. Rev.*, 1952, **6**, 90) and is justified in the present instance by the correlation exhibited in Fig. 1. The relation of partial rate factors is therefore:

$$RT \log k_1/k_2 = a(A_2 - A_1) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where the constant a might vary with the nature of the attacking radical. Kooyman and Farenhorst's results for radical reactivities of hydrocarbons towards trichloromethyl radicals at 91° (*Nature*, 1952, **169**, 153; *Trans. Faraday Soc.*, 1953, **49**, 58) may be used to determine a. In Fig. 1 their data for logarithmic partial rate factors are plotted against A_r for the relevant positions in the hydrocarbons. Some corrections to the partial rate factors have been made in view of more recent work on diphenyl (Cadogan, Hey, and Williams, *J.*, 1954, 794) and the fact that, if localization energies are considered, positions 9 and 10 of phenanthrene are the most reactive so that the reaction rate for position 9 is one-half of the total molecular rate, and not one-quarter as assumed by Kooyman and Farenhorst. The slope of the line in Fig. 1 is 7·5 kcal./β. This value for a means that quite small differences in localization energies correspond to appreciable differences in rates of chemical attack; *e.g.*, if two positions differ in localization energy by 0·03β, one will be attacked twice as fast as the other at 91°.

The above value of a is appropriate for attack by trichloromethyl radicals. Experiments by Dunn, Waters, and Roitt (*J.*, 1954, 580) showed that approximately the same value is suitable for benzoyl radicals. Therefore it is reasonable to assume, in the absence of more definite evidence, that a similar value may be employed when the attack is by phenyl radicals.

From this value of a the experimental partial rate factors (relative to a benzene position) for positions 2, 3, and 4 in pyridine may be converted into localization-energy differences (from the value for a benzene position, −2·5359β). These are listed in the accompanying Table.

Reactivities of pyridine positions at 80°.

Position	Partial rate relative to a benzene position	$RT \log k$	"Experimental" atom-localization energy
2	1·91	0·197	2·510 (−β)
3	0·86	−0·046	2·542
4	1·01	0·003	2·536

It seems reasonable to attribute an experimental uncertainty of about 10% to the measured partial rate factors, which corresponds to an uncertainty in the "experimental" localization energies of $\pm 0{\cdot}004\beta$.

A contour plot of the value of h and k which produce theoretical localization energies for each of the positions covering the "experimental" range of values is given in Fig. 2. This was obtained by preparing a series of graphs of localization energies as a function of k^2 for various constant values of h and reading from the graphs the values of k which corresponded to the two extremes of "experimental" localization energies.

From Fig. 2 it is seen that the three "experimental" localization energies of the Table are obtained only when values of h and k falling in two very small regions of the (h,k) plane are used in the theoretical calculations. These two regions are around the points (i) $h = 0{\cdot}5$, $k = 1$ and (ii) $h = -0{\cdot}5$, $k = 1$. The second of these regions must be rejected because negative values of h correspond to a nitrogen atom's being less electronegative than carbon, which is physically unacceptable. Therefore the calculated atom-localization energies can be brought into agreement with the observed radical reactivities of the pyridine positions only if numerical values of the parameters close to $h = +0{\cdot}5$, $k = 1$, are used.

FIG. 1. *Relation between localization energies and rates of attack by trichloromethyl radicals.*

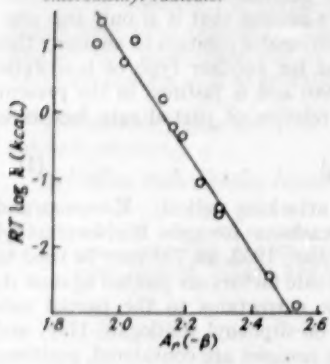
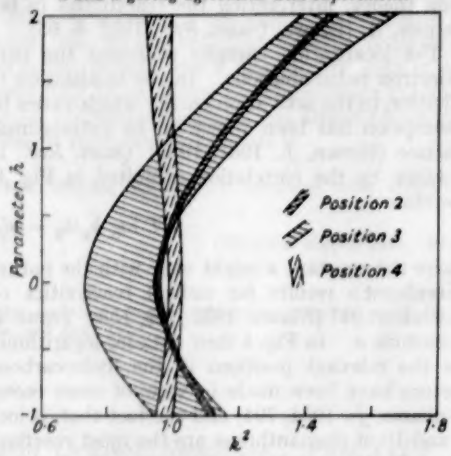


FIG. 2. *Values of the molecular-orbital parameters h and k giving agreement with experiment.*



It is interesting that these values are in reasonable agreement with those derived by other considerations. For example, calculations of dipole moments have been used to derive a value of 0·6 for h (Lowdin, *J. Chem. Phys.*, 1951, **19**, 1323; cf. Odiot and Roux, *J. Chim. phys.*, 1953, **50**, 141) while thermochemical considerations have been used to deduce a value of 1·2 for k (Orgel, Cottrell, Dick, and Sutton, *Trans. Faraday Soc.*, 1951, **47**, 113). However the present values are to be preferred for calculations pertaining to chemical reactivities. Certain defects in the simple molecular-orbital method are ameliorated by adjustment of the parameters to optimum values and there is no reason why the best values for dipole-moment calculations, for example, should also be the best values for calculations of chemical reactivity.

It is also of interest that the simple molecular-orbital approximation is capable of reproducing theoretical rates of attack of pyridine in excellent agreement with experiment when the major hetero-parameters are suitably chosen. The disagreement between theory and experiment, discussed by Hey and Williams (*loc. cit.*) and by Maccoll (*Discuss. Faraday Soc.*, 1953, **14**, 251), is to be ascribed to poor selection of the parameters for pyridine. It is likely that similar agreement between theory and experiment could be obtained for the benzene derivatives studied by Hey, Williams, and their co-workers by a suitable choice of parameters, at least so far as the sterically unhindered *meta*- and *para*-positions are concerned.

Levy and Szwarc (*J. Amer. Chem. Soc.*, 1955, **77**, 1949) have shown that the parameter

a of equation (1) has a value for attack by methyl radicals appreciably different from that for attack by trichloromethyl radicals. It is possible therefore that the value of a used above for phenyl radicals is not the most appropriate. If so, the values derived above for the hetero-atom parameters may need revision. For this reason an experimental study of reactivities of phenyl radicals towards polycyclic aromatic hydrocarbons would be important for the development of the theory of radical reactivities.

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59. *Binding in Some Diatomic Molecules.*

By J. W. LINNETT.

The electronic configurations of a number of states of C_2, N_2, N_2^+, O_2, and O_2^+ have been considered and it has been shown that it is possible, and in some ways convenient, to describe them in terms of a combination of atomic and molecular orbitals. On this basis the number of electrons having a high probability of being between the two nuclei has been assessed for the various states and it has been shown that, to a good approximation, the bond lengths, relative to the Pauling single-bond lengths, are dependent (*a*) on the number of bond electrons, and (*b*) on the way in which these are distributed between σ and π orbitals. A similar behaviour is found for the force constants. The molecules CN, CO, CO^+, and NO have been examined with analogous results. The electronic configurations of maximum probability have been derived, and those of O_2 and other molecules considered. The stability of NO and other odd-electron molecules has been discussed.

THE purpose of this paper is to consider the electron configuration of some of the ground and excited states of the diatomic molecules and molecular ions derived from carbon, nitrogen, and oxygen atoms; and to see how the binding, as assessed by the bond length and vibration frequency, is related to the configuration. The symmetric molecules and ions will be considered first, and then CN, CO, CO^+, and NO.

The lowest-lying orbitals of these diatomic molecules may be represented, in order of binding, by σ_1, σ_2, π_1, σ_3, π_2, σ_4, the two orbitals occupied by the K-electron pairs of each atom being omitted from this series. For symmetrical diatomic molecules these six orbitals have additional symmetry and are written as σ_g, σ_u, π_u, σ_g, π_g, σ_u. The first two, σ_1 and σ_2 (or σ_g and σ_u), may be regarded as being derived mainly from the 2*s* atomic orbitals of the component atoms (though see p. 284) and, for those states of the diatomic molecules derived from C, N, and O which are considered here, electrons in these molecular orbitals do not seem, from what follows, to affect the equilibrium bond lengths and force constants appreciably (see p. 285). Electrons in the next two orbitals, π_1 and σ_3 (π_u and σ_g), are bonding. These two orbitals may be regarded as being derived primarily from the $2p\pi$ and $2p\sigma$ atomic orbitals. Electrons in the last two orbitals, π_2 and σ_4 (π_g and σ_u), are antibonding. They are also derived primarily from the $2p\pi$ and $2p\sigma$ atomic orbitals.

Orbitals of the Diatomic Molecules.—Let us consider the orbitals π_1 and π_2 of the molecule AB. There are two degenerate π_1 orbitals, which may be designated by π_1^+ and π_1^-, the Φ part of the two functions being $e^{+i\phi}$ and $e^{-i\phi}$ respectively, where ϕ is the azimuthal angle. Similarly, there are π_2^+ and π_2^- orbitals. Now it is usual, to a first approximation, to suppose that the molecular orbitals π_1^+ and π_2^+ can be represented satisfactorily by combining together atomic orbitals in the following way

$$\pi_1^+ = a \,.\, 2p\pi_A^+ + b \,.\, 2p\pi_B^+$$

and

$$\pi_2^+ = a' \,.\, 2p\pi_A^+ - b' \,.\, 2p\pi_B^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where a, b, a', and b' are all positive. If the molecule is symmetrical and A is the same as B, then

$$a = b \text{ and } a' = b' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Suppose two electrons with parallel spin occupy the orbitals π_1^+ and π_2^+ and, for the moment, that there are only two electrons in the molecule. The wave function describing this situation and satisfying the Pauli principle is

$$\begin{vmatrix} \pi_1^+(1) \cdot \alpha(1) & \pi_2^+(1) \cdot \alpha(1) \\ \pi_1^+(2) \cdot \alpha(2) & \pi_2^+(2) \cdot \alpha(2) \end{vmatrix} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

both electrons, 1 and 2, having the same spin wave function, represented by $\alpha(1)$ and $\alpha(2)$. By the usual methods of handling determinants it is easy to show that (3) is identical with

$$\begin{vmatrix} 2p\pi_A^+(1) \cdot \alpha(1) & 2p\pi_B^+(1) \cdot \alpha(1) \\ 2p\pi_A^+(2) \cdot \alpha(2) & 2p\pi_B^+(2) \cdot \alpha(2) \end{vmatrix} \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Thus, to describe these two electrons as occupying the $2p\pi_A^+$ and $2p\pi_B^+$ atomic orbitals on the separate atoms is the same as saying that they occupy the π_1^+ and π_2^+ molecular orbitals, for, since (3) and (4) are equal, they represent the same spatial distribution. In fact, because the atomic orbitals are only of considerable magnitude in different regions of space whereas the two molecular orbitals probably have considerable (absolute) magnitude in the same regions, the atomic description in (4) brings out more clearly the actual spatial distribution, the configuration of high probability being that in which the two electrons are on separate atoms. The above provides an example of the way in which two electrons having parallel spins tend to separate as far from one another as is consistent with maintaining a low average potential energy (see Lennard-Jones, Hall, and Pople, *Proc. Roy. Soc.*, 1949, *A*, **198**, 1, **14**; 1950, *A*, **202**, 155, **166**, 323, **336**). The above considerations enable one to see easily why the antibonding effect of an electron in the orbital π_2^+ cancels any bonding effect of an electron in the orbital π_1^+ for the two electrons "force" one another from the region between the two nuclei where it is necessary for their distribution function to have a high value if they are to contribute to the binding together of the two atoms.

Some States of Symmetric Molecules.—The electronic configurations of some of the known states of C_2, N_2, O_2, N_2^+, and O_2^+ will be considered. The states that have been examined are those for which the bond lengths and vibration frequencies (and, hence, force constants) are known with considerable certainty, and for which the electronic structures are fairly reliably known. Unfortunately, it is not possible to be as certain of the latter, in many cases, as of the former. Consideration has been restricted to the more low-lying states since, for those, interaction between different electronic states is not likely to be large (cf. Ross, *Trans. Faraday Soc.*, 1952, **48**, 973) for they are more widely separated on an energy scale than the more highly excited states. The results for seven states of C_2, five of N_2, two of N_2^+, five of O_2, and four of O_2^+ are listed in Table 1. Col. 1 lists the electronic state of the molecule; col. 2 gives the distribution of the electrons among the molecular orbitals; col. 3 gives a more detailed representation of the way in which the electrons may be regarded as being distributed among the various orbitals, each occupied state being listed individually. In col. 3 the conclusions of the last section have been adopted and the representation in terms of atomic orbitals is used wherever possible (*i.e.*, instead of writing $\pi_u^+ \cdot \pi_g^+$ for two electrons with parallel spins in these orbitals, this column gives $2p\pi_A^+ \cdot 2p\pi_B^+$ which is completely equivalent to it). Also, in this column, the spins of the electrons occupying the various states are indicated. The presence of an electron in a $2s_A$ orbital with a β-spin function is represented by $\overline{2s_A}$, while if an electron in the same state is associated with an α-spin wave function the bar over the $2s_A$ is omitted. In some cases two or more representations would apply to a given state equally well, and the complete wave function is then a combination of the wave functions corresponding to these representations; for instance, for the $^1\Sigma_g^+$ state of O_2 a combination of

$$2s_A \cdot \overline{2s_A} \cdot 2s_B \cdot \overline{2s_B} \cdot 2p\pi_A^+ \cdot 2p\pi_B^+ \cdot \overline{2p\pi_A^-} \cdot \overline{2p\pi_B^-} \cdot \overline{\pi_u^+} \cdot \pi_u^- \cdot \sigma_g \cdot \overline{\sigma_g}$$

and

$$2s_A \cdot \overline{2s_A} \cdot 2s_B \cdot \overline{2s_B} \cdot \overline{2p\pi_A^+} \cdot \overline{2p\pi_B^+} \cdot 2p\pi_A^- \cdot 2p\pi_B^- \cdot \pi_u^+ \cdot \overline{\pi_u^-} \cdot \sigma_g \cdot \overline{\sigma_g}$$

In such circumstances only one has been given. The two exceptions to this are the $^3\Sigma_u^+$ and $^3\Sigma_u^-$ states of O_2 for which it is necessary to give the appropriate sum and difference

TABLE 1. *Values of the equilibrium bond lengths (r_e) and force constants (k_e) for different electronic states of some homopolar molecules with their electronic configurations. The scaling factors r_1 (Pauling's single-bond length), r_2, k_1, and k_2 are listed in Table 3. The spatial distribution of the electrons is indicated in col. 10 (see text).*

Electronic state	Summary	Electronic configuration: Detail	r_e	k_e	r_e/r_1	r_e/r_2	k_e/k_1	k_e/k_2	Electron pattern
C_2 molecule.									
d $^1\Sigma_u^+$	$\sigma_g^2.\sigma_u.\pi_u^4.\sigma_g$	$2s_A.2s_B.\overline{\sigma_g}(\pi_u^+.\overline{\pi_u^+}.\pi_u^-.\overline{\pi_u^-}.\overline{\sigma_g})$	1·2378	11·831	0·804	0·975	2·517	1·035	$sp^2(\pi^2)$; $s^1p^3(\sigma\pi^2)$
c $^1\Pi_g$	$\sigma_g^2.\sigma_u.\pi_u^3.\sigma_g^2$	$2s_A.2s_B.\overline{\sigma_g}(\pi_u^+.\overline{\pi_u^+}.\overline{\pi_u^-}.\sigma_g.\overline{\sigma_g})$	1·2730	11·568	0·827	1·003	2·461	1·012	$sp^2(\sigma\pi)$; $s^1p^3(\sigma\pi^2)$
b $^1\Pi_u$	$\sigma_g^2.\sigma_u^2.\pi_u^3.\sigma_g$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}(\pi_u^+.\overline{\pi_u^+}.\pi_u^-.\overline{\sigma_g})$	1·3180	9·143	0·856	1·038	1·945	0·800	$sp^2(\pi^2)$; $sp^2(\sigma\pi)$
a $^1\Sigma_g^+$	$\sigma_g^2.\sigma_u^2.\pi_u^4$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}(\pi_u^+.\overline{\pi_u^+}.\pi_u^-.\overline{\pi_u^-})$	1·2422	12·171	0·807	0·979	2·590	1·064	$sp^2(\pi^2)$; $sp^2(\pi^2)$
B $^3\Pi_g$	$\sigma_g^2.\sigma_u^2.\pi_u^3.\sigma_g.\pi_g$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}.2p\pi_A^+.2p\pi_B^+(\overline{\pi_u^-}\sigma_g)$	1·5350	4·328	0·997	1·209	0·921	0·378	$sp^2(\sigma)$; $sp(\pi)$
A $^3\Pi_g$	$\sigma_g^2.\sigma_u.\pi_u^3.\sigma_g^2$	$2s_A.2s_B.\overline{\sigma_g}(\pi_u^+.\overline{\pi_u^+}.\pi_u^-.\sigma_g.\overline{\sigma_g})$	1·2660	11·303	0·822	0·997	2·405	0·988	$sp^2(\sigma\pi^2)$; $s^1p^3(\sigma\pi)$
X $^3\Pi_u$	$\sigma_g^2.\sigma_u^2.\pi_u^3.\sigma_g$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}(\pi_u^+.\overline{\pi_u^+}.\pi_u^-.\sigma_g)$	1·3117	9·522	0·852	1·033	2·026	0·837	$sp^2(\sigma\pi^2)$; $sp(\pi)$
N_2 molecule.									
C $^3\Pi_u$	$\sigma_g^2.\sigma_u.\pi_u^4.\sigma_g^2.\pi_g$	$2s_A.2s_B.\overline{\sigma_g}.2p\pi_A^+.2p\pi_B^+(\overline{\pi_u^+}.\pi_u^-.\overline{\pi_u^-}.\sigma_g.\overline{\sigma_g})$	1·1482	17·082	0·820	1·000	2·847	1·000	$sp^2(\sigma\pi)$; $s^1p^3(\sigma\pi^2)$
B $^3\Pi_g$	$\sigma_g^2.\sigma_u^2.\pi_u^4.\sigma_g.\pi_g$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}.2p\pi_A^+.2p\pi_B^+(\overline{\pi_u^+}.\pi_u^-.\overline{\pi_u^-}.\sigma_g)$	1·2123	12·403	0·866	1·056	2·067	0·726	$sp^2(\sigma\pi)$; $sp^2(\pi^2)$
A $^3\Sigma_u^+$	$\sigma_g^2.\sigma_u^2.\pi_u^3.\sigma_g^2.\pi_g$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}.2p\pi_A^+.2p\pi_B^+(\pi_u^-.\overline{\pi_u^-}.\sigma_g.\overline{\sigma_g})$	1·293	8·796	0·924	1·126	1·466	0·515	$sp^2(\sigma\pi)$; $sp^2(\sigma\pi)$
a $^1\Pi_g$	$\sigma_g^2.\sigma_u^2.\pi_u^4.\sigma_g.\pi_g$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}.2p\pi_A^+.2p\pi_B^+(\overline{\pi_u^+}.\pi_u^-.\overline{\pi_u^-}.\overline{\sigma_g})$	1·213	11·808	0·866	1·057	1·968	0·691	$sp^2(\sigma\pi^2)$; $sp^2(\pi)$
X $^1\Sigma_g^+$	$\sigma_g^2.\sigma_u^2.\pi_u^4.\sigma_g^2$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}(\pi_u^+.\overline{\pi_u^+}.\pi_u^-.\overline{\pi_u^-}.\sigma_g.\overline{\sigma_g})$	1·094	22·964	0·781	0·953	3·827	1·344	$sp^2(\sigma\pi^2)$; $sp^2(\sigma\pi^2)$
N_2^+ ion.									
B $^2\Sigma_u^+$	$\sigma_g^2.\sigma_u.\pi_u^4.\sigma_g^2$	$2s_A.2s_B.\overline{\sigma_g}(\pi_u^+.\overline{\pi_u^+}.\pi_u^-.\overline{\pi_u^-}.\sigma_g.\overline{\sigma_g})$	1·075	24·151	0·767	0·936	4·025	1·414	$sp^2(\sigma\pi^2)$; $s^1p^3(\sigma\pi^2)$
X $^2\Sigma_g^+$	$\sigma_g^2.\sigma_u^2.\pi_u^4.\sigma$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}(\pi_u^+.\overline{\pi_u^+}.\pi_u^-.\overline{\pi_u^-}.\sigma_g)$	1·1162	20·093	0·797	0·972	3·349	1·176	$sp^2(\sigma\pi^2)$; $sp^2(\sigma\pi)$
O_2 molecule.									
B $^3\Sigma_u^-$	$\sigma_g^2.\sigma_u^2.\pi_u^3.\sigma_g^2.\pi_g^3$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}.2p\pi_A^+.2p\pi_B^+.2p\pi_A^-.2p\pi_B^-[\overline{\pi_u^+}.\overline{\pi_g^-} - \overline{\pi_u^-}.\overline{\pi_g^+}](\sigma_g.\overline{\sigma_g})$	1·604	2·311	1·215	1·429	0·308	0·139	$sp^2(\sigma)$; $sp(p^2)^1(\sigma)$
A $^3\Sigma_u^+$	$\sigma_g^2.\sigma_u^2.\pi_u^3.\sigma_g^2.\pi_g^3$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}.2p\pi_A^+.2p\pi_B^+.2p\pi_A^-.2p\pi_B^-[\overline{\pi_u^+}.\overline{\pi_g^-} + \overline{\pi_u^-}.\overline{\pi_g^+}](\sigma_g.\overline{\sigma_g})$	1·42	3·160	1·076	1·265	0·421	0·191	$sp^2(\sigma)$; $sp^2(\sigma)$
b $^1\Sigma_g^+$	$\sigma_g^2.\sigma_u^2.\pi_u^4.\sigma_g^2.\pi_g^2$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}.2p\pi_A^+.2p\pi_B^+.2p\pi_A^-.2p\pi_B^-(\overline{\pi_u^+}.\pi_u^-.\sigma_g.\overline{\sigma_g})$	1·2268	9·670	0·929	1·094	1·289	0·583	$sp^2(\sigma\pi)$; $sp^2(\sigma\pi)$
a $^1\Delta_g$	$\sigma_g^2.\sigma_u^2.\pi_u^4.\sigma_g^2.\pi_g^2$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}.2p\pi_A^+.2p\pi_B^+.2p\pi_B^-(\pi_u^+.\overline{\pi_u^-}.\sigma_g.\overline{\sigma_g})$	1·2155	10·732	0·921	1·083	1·431	0·647	$sp^2(\sigma\pi)$; $sp^2(\sigma\pi)$
X $^3\Sigma_g^-$	$\sigma_g^2.\sigma_u^2.\pi_u^4.\sigma_g^2.\pi_g^2$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}.2p\pi_A^+.2p\pi_B^+.2p\pi_A^-.2p\pi_B^-(\overline{\pi_u^+}.\overline{\pi_u^-}.\sigma_g.\overline{\sigma_g})$	1·2074	11·766	0·915	1·075	1·569	0·709	$sp^2(\sigma\pi^2)$; $sp^2(\sigma)$
O_2^+ ion.									
b $^4\Sigma_g^-$	$\sigma_g^2.\sigma_u^2.\pi_u^4.\sigma_g.\pi_g^2$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}.2p\pi_A^+.2p\pi_B^+.2p\pi_A^-.2p\pi_B^-(\overline{\pi_u^+}.\overline{\pi_u^-}.\sigma_g)$	1·2795	6·748	0·969	1·140	0·900	0·407	$sp^2(\sigma)$; $sp^2(\pi^2)$
A $^2\Pi_u$	$\sigma_g^2.\sigma_u^2.\pi_u^3.\sigma_g^2.\pi_g^2$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}.2p\pi_A^+.2p\pi_B^+.\overline{2p\pi_A^-}.\overline{2p\pi_B^-}(\pi_u^+.\sigma_g.\overline{\sigma_g})$	1·4089	3·816	1·067	1·255	0·509	0·230	$sp^2(\sigma\pi)$; $sp^2(\sigma)$
a $^4\Pi_u$	$\sigma_g^2.\sigma_u^2.\pi_u^3.\sigma_g^2.\pi_g^2$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}.2p\pi_A^+.2p\pi_B^+.2p\pi_A^-.2p\pi_B^-(\pi_u^+.\sigma_g.\overline{\sigma_g})$	1·3813	5·053	1·046	1·230	0·674	0·305	$sp^2(\sigma)$; $sp^2(\sigma\pi)$
X $^2\Pi_g$	$\sigma_g^2.\sigma_u^2.\pi_u^4.\sigma_g^2.\pi_g$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}.2p\pi_A^+.2p\pi_B^+(\overline{\pi_u^+}.\pi_u^-.\overline{\pi_u^-}.\sigma_g.\overline{\sigma_g})$	1·1227	16·587	0·851	1·000	2·212	1·000	$sp^2(\sigma\pi^2)$; $sp^2(\sigma\pi)$

TABLE 2. *Values of the equilibrium bond lengths (r_e) and force constants (k_e) for different electronic states of some heteropolar molecules with their electronic configurations. The scaling factors r_1, r_2, k_1, and k_2 are listed in Table 3. The spatial distribution of the electrons is indicated in col. 10 (see text).*

Electronic state	Electronic configuration: Summary	Detail	r_e	k_e	r_e/r_1	r_e/r_2	k_e/k_1	k_e/k_2	Electron pattern
CN molecule.									
B $^2\Sigma^+$	$\sigma_1^2.\sigma_2^2.\pi_1^4.\sigma_3^1$	$2s_A.\overline{2s_A}.2s_B.\overline{\sigma_3}(\pi_1^+.\overline{\pi_1^+}.\pi_1^-.\overline{\pi_1^-}.\sigma_3.\overline{\sigma_3})$	1·1506	17·829	0·777	0·933	**3·639**	1·423	$sp^3(\sigma\pi^2)$; $s^1p^3(\sigma\pi^2)$
A $^2\Pi_i$	$\sigma_1^2.\sigma_2^2.\pi_1^3.\sigma_3^2$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}(\pi_1^+.\overline{\pi_1^+}.\pi_1^-.\sigma_3.\overline{\sigma_3})$	1·2327	12·533	0·832	1·000	2·558	1·000	$sp^3(\sigma\pi^2)$; $sp^3(\sigma\pi)$
X $^2\Sigma^+$	$\sigma_1^2.\sigma_2^2.\pi_1^4.\sigma_3$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}(\pi_1^+.\overline{\pi_1^+}.\pi_1^-.\overline{\pi_1^-}.\sigma_3)$	1·1718	16·291	0·792	0·951	3·325	1·300	$sp^3(\sigma\pi^2)$; $sp^3(\pi^2)$
CO molecule.									
a' $^3\Sigma^+$	$\sigma_1^2.\sigma_2^2.\pi_1^3.\sigma_3^1.\pi_3$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}.2p\pi_A^+.2p\pi_B^+(\pi_1^-.\overline{\pi_1^-}.\sigma_3.\overline{\sigma_3})$	1·359	5·992	0·924	1·106	1·362	0·573	$sp^3(\sigma\pi)$; $sp^2(\sigma\pi)$
a $^3\Pi_r$	$\sigma_1^2.\sigma_2.\pi_1^4.\sigma_3^1.\pi_3$	$2s_A.2s_B.\overline{\sigma_3}.2p\pi_A^+.2p\pi_B^+(\overline{\pi_1^+}.\pi_1^-.\overline{\pi_1^-}.\sigma_3.\overline{\sigma_3})$	1·2093	12·218	0·823	0·984	2·777	1·169	$sp^3(\sigma\pi)$; $s^1p^3(\sigma\pi^2)$
A $^1\Pi$	$\sigma_1^2.\sigma_2.\pi_1^4.\sigma_3^1.\pi_3$	$2s_A.2s_B.\overline{\sigma_3}.\overline{2p\pi_A^+}.\overline{2p\pi_B^+}(\pi_1^+.\pi_1^-.\overline{\pi_1^-}.\sigma_3.\overline{\sigma_3})$	1·2351	9·278	0·840	1·005	2·109	0·888	$sp^3(\sigma\pi^2)$; $s^1p^3(\sigma\pi)$
X $^1\Sigma^+$	$\sigma_1^2.\sigma_2^2.\pi_1^4.\sigma_3^2$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}(\pi_1^+.\overline{\pi_1^+}.\pi_1^-.\overline{\pi_1^-}.\sigma_3.\overline{\sigma_3})$	1·1282	19·023	0·767	0·918	4·323	1·820	$sp^3(\sigma\pi^2)$; $sp^3(\sigma\pi^2)$
CO^+ ion.									
B $^2\Sigma^+$	$\sigma_1^2.\sigma_2^2.\pi_1^4.\sigma_3$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}(\pi_1^+.\overline{\pi_1^+}.\pi_1^-.\overline{\pi_1^-}\sigma_3)$	1·1687	12·146	0·795	0·951	2·761	1·162	$sp^3(\sigma\pi^2)$; $sp^2(\pi^2)$
A $^2\Pi_i$	$\sigma_1^2.\sigma_2^2.\pi_1^3.\sigma_3^2$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}(\pi_1^+.\overline{\pi_1^+}.\pi_1^-.\sigma_3.\overline{\sigma_3})$	1·2437	9·855	0·846	1·012	2·240	0·943	$sp^3(\sigma\pi^2)$; $sp^2(\sigma\pi)$
X $^2\Sigma^+$	$\sigma_1^2.\sigma_2.\pi_1^4.\sigma_3^2$	$2s_A.2s_B.\overline{\sigma_2}(\pi_1^+.\overline{\pi_1^+}.\pi_1^-.\overline{\pi_1^-}.\sigma_3.\overline{\sigma_3})$	1·1151	19·802	0·759	0·907	4·500	1·895	$sp^3(\sigma\pi^2)$; $s^1p^3(\sigma\pi^2)$
NO molecule.									
B $^2\Pi_r$	$\sigma_1^2.\sigma_2^2.\pi_1^3.\sigma_3^1.\pi_3^2$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}.2p\pi_A^+.2p\pi_B^+.\overline{2p\pi_A^-}.\overline{2p\pi_B^-}(\overline{\pi_1^+}.\sigma_3.\overline{\sigma_3})$	1·385 1·448	4·743 4·730	1·011 1·057	1·204 1·258	0·753 0·751	0·297 0·297	$sp^3(\sigma\pi)$; $sp^2(\sigma)$ —
X $^2\Pi_{\frac{1}{2}}$ $^2\Pi_{\frac{3}{2}}$	$\sigma_1^2.\sigma_2^2.\pi_1^4.\sigma_3^1.\pi_3$	$2s_A.\overline{2s_A}.2s_B.\overline{2s_B}.2p\pi_A^+.2p\pi_B^+(\overline{\pi_1^+}.\pi_1^-.\overline{\pi_1^-}.\sigma_3.\overline{\sigma_3})$	1·1508 —	15·940 15·946	0·840 —	1·000 —	2·530 2·531	1·000 1·000	$sp^3(\sigma\pi^2)$; $sp^3(\sigma\pi)$ —

combinations of the wave functions corresponding to the basic representations (see p. 280). In Table 1 the occupied orbitals having large values in the region between the atoms, the electrons in which are therefore bonding, are enclosed in parentheses. In col. 4 of Table 1 the observed equilibrium internuclear distances r_e are listed. These are taken from Herzberg ("Molecular Spectra and Molecular Structure of Diatomic Molecules," Van Nostrand Co. Inc., 1950). Col. 5 gives the force constants k_e derived from the observed vibration frequencies which are also taken from Herzberg (*op. cit.*). In col. 6 the bond lengths listed in col. 4 are divided by the C–C, N–N, and O–O single-bond lengths r_1

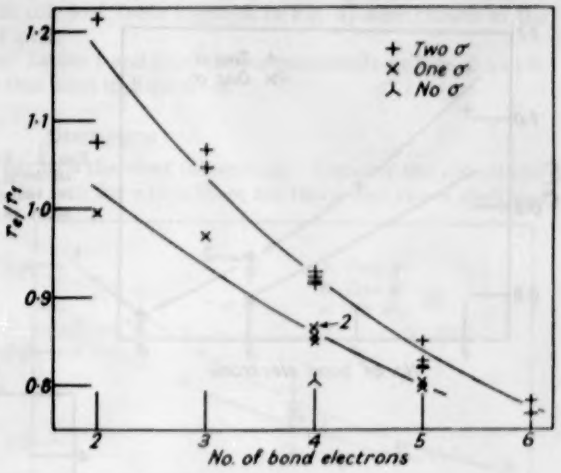


FIG. 1. *Graph of r_e/r_1 against the number of bond electrons for C_2, N_2, N_2^+, O_2, and O_2^+, when r_1 (Pauling's single-bond length) has the values listed in Table 3.*

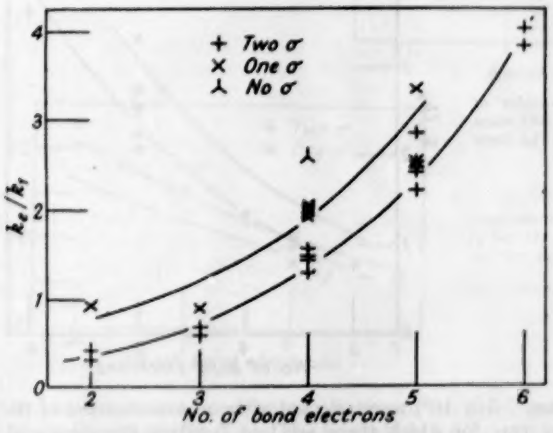


FIG. 2. *Graph of k_e/k_1 against the number of bond electrons for C_2, N_2, N_2^+, O_2, and O_2^+, when k_1 has the values listed in Table 3.*

given by Pauling (1·54, 1·40, and 1·52 Å, respectively; "Nature of the Chemical Bond," Cornell Univ. Press, 1939, p. 167). In col. 7 another scaling procedure has been carried out on the bond lengths by using as standards the bond lengths (or mean of several) for those structures in which bonding is by two σ_g and three π_u electrons * [for CC, NN, and OO, these are 1·2695 (mean of two values), 1·1482, and 1·1227 Å respectively]. In col. 8 a procedure analogous to that in col. 6 has been carried out for the force constants of col 5. The scaling constants, arbitrarily chosen (see p. 280), are 4·7, 6·0, and 7·2 × 10^5 dynes cm.$^{-1}$

* The sole reason for choosing this group of bonding electrons is that it alone is to be found in some state binding together CC, NN, OO, CN, CO, and NO.

for CC, NN, and OO. In col. 9 a procedure similar to that in col. 7 has been carried out on the force constants, the three scaling constants being 11·435, 17·082, and 16·587 × 10^5 dynes cm.$^{-1}$. Col. 10 is explained in the Discussion (p. 283).

The data in cols. 6 and 8 of Table 1 are presented graphically in Figs. 1 and 2, in both of which the points for states in which two, one, or none of the bonding electrons are σ_g electrons are represented differently. In obtaining the results presented in Fig. 1 it was not unnatural to attempt to scale the data for the different molecules according to Pauling's values for single-bond lengths (the exact values used would not be critical). For the force-constant results in Fig. 2 an effort was made to treat them in an analogous manner. The

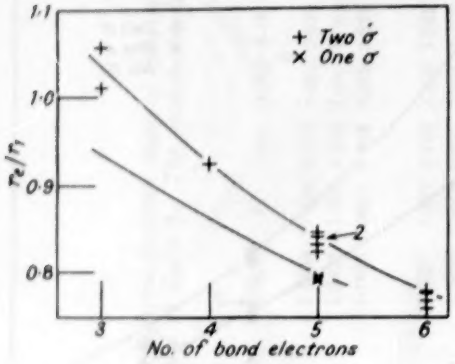


FIG. 3. *Graph of r_e/r_1 against the number of bond electrons for* CN, CO, CO^+, *and* NO *when r_1 has the values listed in Table* 3. (The lines are the same as in Fig. 1.)

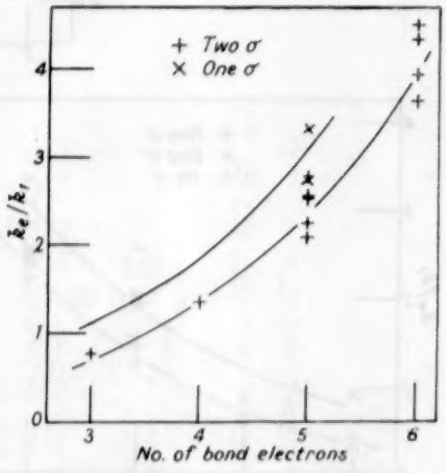


FIG. 4. *Graph of k_e/k_1 against the number of bond electrons for* CN, CO, CO^+, *and* NO *when k_1 has the values listed in Table* 3. (The lines are the same as in Fig. 2.)

standard values chosen (4·7, 6·0, and 7·5 × 10^5) were selected after an examination of the force constants and electronic structure for which there are four bonding electrons and, unlike the normal single-bond lengths used for Fig. 1, these three figures are arbitrary. The results in both Figures will be considered in the Discussion.

In Table 1 it will be seen that the $^3\Sigma_u^+$ and $^3\Sigma_u^-$ states of O_2 are described as having two bonding electrons. The reason for this is as follows. If the combination $(\pi_u^+ \cdot \pi_g^- - \pi_u^- \cdot \pi_g^+)$ is multiplied out, it is found to be equal to $[2p\pi_A(i) \cdot 2p\pi_A(j) - 2p\pi_B(i) \cdot 2p\pi_B(j)]\sin(\phi_i - \phi_j)$, while $(\pi_u^+ \cdot \pi_g^- + \pi_u^- \cdot \pi_g^+)$ equals $[2p\pi_A(i) \cdot 2p\pi_B(j) - 2p\pi_A(j) \cdot 2p\pi_B(i)]\cos(\phi_i - \phi_j)$, where i and j are the two electrons and $2p\pi_A$ is that part of $2p\pi_A^+$ and $2p\pi_A^-$ which is independent of ϕ. The electrons in these orbitals do not contribute to the bond, and therefore the only bond electrons are the two in the σ_g orbital.

The $^3\Sigma_u^-$ state involves a combination of ionic states, so it is not surprising that it has a higher energy than the $^3\Sigma_u^+$ state in which the pair of electrons in these orbitals have a high probability of being on the separate atoms.

Some States of Heteropolar Molecules.—Data for some states of CN, CO, CO^+, and NO are given in Table 2, the same columns being used as in Table 1. The results in cols. 6 and 8 are shown graphically in Figs. 3 and 4, the lines being drawn in these graphs to be identical with those of Figs. 1 and 2 respectively. The single-bond lengths used for scaling (1·48 for CN, 1·47 for CO and CO^+, and 1·37 for NO) were chosen to bring the results for these molecules in Fig. 3 most closely in line with those for the symmetric molecules in Fig. 1. The force constant scaling factors in col. 8 of Table 2 (graph in Fig. 4) were chosen in the same way relative to the results in Fig. 2.

The data listed in cols. 7 and 9 of Tables 1 and 2 are shown graphically in Figs. 5 and 6, the representation being similar to that used in Figs. 1—4.

Discussion

The results shown in Fig. 1 are perhaps the most interesting. Consider the nine states involving four bonding electrons. The four for which there are two σ and two π electrons

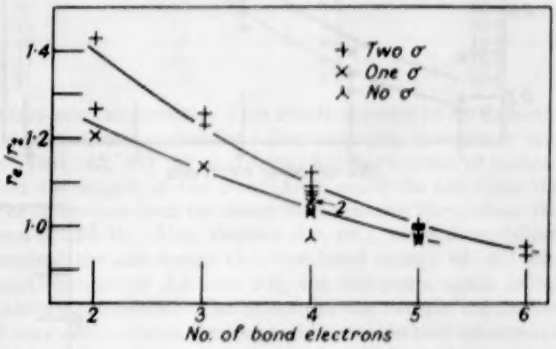


Fig. 5a. *Graph of r_e/r_2 against the number of bond electrons for C_2, N_2, N_2^+, O_2, and O_2^+ when r_2 has the values listed in Table 3.*

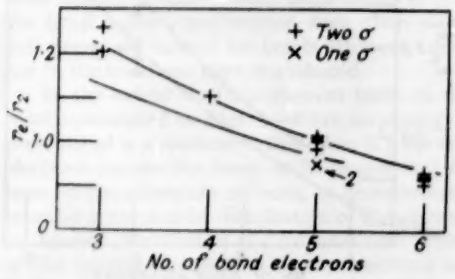


Fig. 5b. *Graph of r_e/r_2 against the number of bond electrons for CN, CO, CO^+, and NO when r_2 has the values listed in Table 3.* (The lines are the same as in Fig. 5a.)

in the bond all have a bond length relative to the single bond length which is close to 0·92 (three for O_2 and one for N_2). The four which have one σ and three π electrons in the bond have a relative bond length of about 0·86 [two are for N_2 (superimposed) and two for C_2]. The state of C_2 with four π but no σ electrons in the bond region has the relative bond length of about 0·81. The same type of behaviour is apparent for the states having five electrons in the bond (*i.e.*, those having two σ electrons form one group having a relative bond length greater than the two having one σ electron in the bond). The situation is the same when there are two and three electrons in the bond though fewer such states are known with these molecules.

In Fig. 1 a smooth curve has been drawn which passes near the points for states involving two σ bonding electrons, and another line, below it, which passes near the points for states

involving only one σ bonding electron. The figure shows that, for a given number of σ electrons in the bond, the length (relative to the Pauling single-bond length) is governed quite closely by the number of electrons in the bond. The variation, for a given electron grouping, seems to become greater the smaller the number of electrons in the bond (cf. the two states of O_2 involving only two bonding electrons). So, as regards equilibrium bond length (relative), there appear to be two main effects. The first, and more important, is the number of electrons in the bond region. The second is that the length depends on the number of σ electrons. The effect of this is quite considerable and is that the bonds are

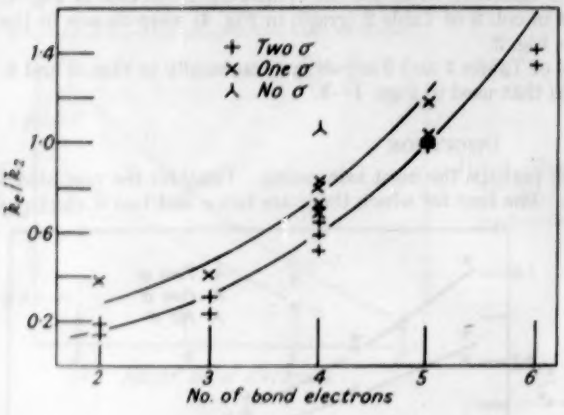


FIG. 6a. *Graph of k_e/k_2 against the number of bond electrons for C_2, N_2, N_2^+, O_2, and O_2^+ when k_2 has the values listed in Table* 3.

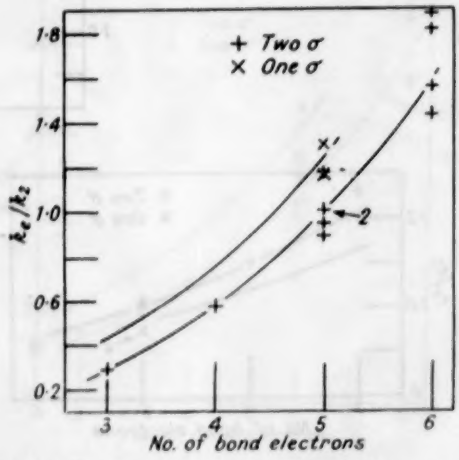


FIG. 6b. *Graph of k_e/k_2 against the number of bond electrons for* CN, CO, CO^+, *and* NO *when k_2 has the values listed in Table* 3. (The lines are the same as in Fig. 6a.)

longer, for a given number of bonding electrons, the more of these that are σ electrons (in Fig. 1 there is no exception to this).

The results in Fig. 3 show that the data for heteropolar molecules are in good agreement with the above, though it must be remembered that arbitrary single-bond lengths were chosen for these molecules. The results in Fig. 5 are also of the same type and are presented here because, for these results, no arbitrary choice was made for the scaling factor for the heteropolar molecules. All scaling factors were chosen in the same way, being the bond length (or mean of several) when two σ and three π electrons are involved in the bond. The disadvantage of this treatment is that it places particular importance on the bond lengths of a few states (*i.e.*, those used as standards).

The analogous data for force constants are presented in Figs. 2, 4, and 6. The general

form of these results is the same as that obtained for bond lengths, though the spread of values for a given electron grouping is greater than for the bond lengths. The scaling constants used in obtaining the data for Figs. 2 and 4 were arbitrarily chosen.

The scaling factors used in the previous sections are summarised in Table 3. As regards the bond lengths, the standard value for AB is, in all instances, greater than the mean of those for AA and BB. This is true for the approach summarised in Figs. 1 and 3, and also for that of Fig. 5. Moreover, the results for the force constants show the same behaviour since the standard force constant for AB is, in all cases, less than the mean of those for AA and BB. Further, in every column of Table 2, the difference from the mean is greater for CO than for CN and NO. This would be expected if it arises from the difference between

TABLE 3. *The scaling factors r_1, r_2, k_1, and k_2 used in Tables 1 and 2, cols. 6—9; data are shown graphically in Figs. 1—6; r_1 and r_2 are in Å, and k_1 and k_2 in units of 10^5 dynes cm.$^{-1}$.*

	Bond lengths		Force constants	
Atom pair	Figs. 1 & 3 Col. 6 (r_1)	Fig. 5 Col. 7 (r_2)	Figs 2 & 4 Col. 8 (k_1)	Fig. 6 Col. 9 (k_2)
CC	1·54	1·27	4·7	11·4
NN	1·40	1·15	6·0	17·1
OO	1·32	1·12	7·5	16·6
CN	1·48	1·23	4·9	12·5
CO	1·47	1·23	4·4	10·5
NO	1·37	1·15	6·3	15·9

the two nuclear charges in the heteropolar molecules. This result appears to be different from that generally accepted for polyatomic molecules. For example, Stevenson and Schomaker (*J. Amer. Chem. Soc.*, **1941**, **63**, 37), in modifying Pauling's scale of normal single-bond lengths, suggested that the length of the bond A–B would be *less* than the mean of those of A–A and B–B, the difference from the mean being greater the greater the electronegativity difference between A and B. Also, Pauling (*loc. cit.*), when formulating his scale of electronegativities, reached the conclusion that the bond energy of AB was greater than the mean of the bond energies of AA and BB, the difference again being greater the greater the electronegativity difference. The reason for the reverse conclusion found here is not easy to see, but it may arise because Pauling and Stevenson and Schomaker were concerned mainly with single bonds in polyatomic molecules in which electrons not in the bond under consideration were often shared with other atoms. The results given in this paper are largely for bonds stronger and shorter than single bonds and the electrons not in the bond are always unshared.

To the extent that the chemist tends to regard σ bonds as stronger than π bonds the results presented in Figs. 1—6 are surprising. However, it has only been shown that the presence of a σ electron rather than a π electron in a bond containing a given number of electrons causes the bond to be longer and to have a lower force constant. There has been no consideration of heats of dissociation. The reason for the results obtained here must lie in the spatial distribution of the electrons and these will now be considered.

Spatial Distribution of Electrons.—An attempt has been made to give some indication of the spatial distribution of the electrons in the various states in the last column of Tables 1 and 2. In the symmetrical molecules the spatial distribution of electrons is symmetrical for all states in the sense that the dipole moment is zero for all states. In the last column of Table 1 the electrons of each spin are described separately. For each spin the distribution at each atom is given for both shared and unshared electrons which are members of this set. For example $sp^3(\sigma\pi)$ means that round each atom there is a group of four electrons, the contributing atomic orbitals being the $2s$ and three $2p$. Of these electrons two are shared with the other atom, one occupying a σ orbital and the other a π orbital (this is half an ordinary double bond). The description $sp^2(\pi)$, which involves five electrons in all, means that the grouping at each atom is sp^2 and that one electron is shared, two being unshared; the one shared is in a π orbital. This is a binding configuration not encountered in polyatomic molecules. Finally, the symbol $s^1p^3(\sigma\pi^2)$ (see $^1\Sigma_u^+$ state of C_2) means that there is a $\sigma_g 2s$ non-bonding electron shared between the two atoms,

that, in addition, each atom is employing three $2p$ orbitals, and that there are three shared electrons in a σ and two π orbitals. Four electrons, in all, are involved in this grouping. The situation is that, at any instant, one atom has three bonding electrons associated with it while the other has three bonding and one lone electron. However, there is an equal probability of each having three and each having four. The mode of representation used in col. 10 of Tables 1 and 2 does not give a complete description of the electron distribution even within its own limitations. For instance, the $^1\Sigma_g^+$ and $^1\Delta_g$ states of O_2 are both described as $sp^3(\sigma\pi)$; $sp^3(\sigma\pi)$, though they involve different distributions. The difference lies in the relation of the electrons of one spin to those of the other. Nevertheless they are of help in visualising the distribution.

Lennard-Jones *et al.* (*loc. cit.*) have shown that the system of two electrons with parallel spin in σ and π bonding orbitals can be described equally well by the equivalent orbitals which are the sum and difference of the more usual σ and π molecular orbitals. The use of equivalent orbitals brings out more clearly the actual spatial arrangement of the electrons, for the most probable configuration is that in which the two bonding electrons are disposed symmetrically each side of the line joining the two atoms and, for symmetrical molecules, half way between them. Similarly, for the triple bond grouping $\sigma\pi^2$ of three electrons having parallel spins the most probable configuration is that in which the three electrons are symmetrically disposed in the form of an equilateral triangle round the line joining the two atoms. Again, Lennard-Jones *et al.* give the appropriate equivalent orbitals. These representations of the double and triple bonds come close to the older representations (*e.g.*, that of Baeyer). Consequently, in the group of six electrons $sp^3(\sigma\pi)$ the most probable configuration is that in which each atom has four electrons of the particular spin under consideration around it, these being arranged at the corners of a tetrahedron which is not far from being regular; of these there are two electrons on each atom which are unshared and two which are shared. For the group $sp^3(\sigma\pi^2)$ each atom has a tetrahedral group of four but one is unshared and three are shared. For $sp^2(\sigma)$ each atom has a group of three disposed, in the configuration of maximum probability, in the form of a triangle round it with two unshared on each atom and one shared between the two atoms. Other arrangements can be visualised on similar lines. The arrangements $sp(\pi)$, $sp^2(\pi)$, and $sp^2(\pi^2)$ (cf. states of N_2 and C_2) are more difficult to describe. In the first there are two electrons of a particular spin round each atom, one of which is shared and one unshared. From the known configuration of maximum probability of two electrons with parallel spins in $2s$ and $2p$ orbitals it would seem that the pair on each atom will be approximately on opposite sides of the nucleus but that the line joining them will be at an angle to the line joining the two atoms, the shared electron being away from the internuclear line in the most probable configuration. The overall, time average, distribution will, of course, be axially symmetrical. The other two arrangements are similar but each involves three electrons round each atom.

On the basis of the above treatment the two σ orbitals (σ_g and σ_u or σ_1 and σ_2) are presumably best described in terms of combinations of $2s$ and $2p\sigma$ atomic hybrids rather than as combinations of the $2s$ atomic orbitals. There is no objection on the basis of symmetry to this, since combination of the $2s$ orbitals leads to σ_g and σ_u orbitals, as does the combination of the $2p\sigma$ atomic orbitals. The hybrids for these two σ orbitals are then those in which the electrons occupying them are located with highest probability on the far side of the atom from the other atom. Being outside the bond region they would not be expected to affect the equilibrium bond length and force constant greatly. That this is so is indicated by the results in Tables 1 and 2. For example, the $^1\Sigma_u^+$ state of C_2 and the $^2\Sigma_g^+$ state of N_2^+ both have the bonding group $(\pi_u^4\sigma_g)$, and the relative bond lengths (col. 6) are 0·804 and 0·797 even though they have different numbers of electrons (3 and 4 respectively) in the lower-lying σ orbitals. Comparison may also be made for the nine states having the bonding group $(\pi^3\sigma^2)$. There are four states for which the σ_1 and σ_2 orbitals (or σ_g and σ_u) are filled and the mean bond length (col. 6) is 0·84. There are five states for which there are three electrons in these two σ orbitals and the mean figure for these is 0·83. The difference is therefore small, though it may indicate that electrons in these orbitals do exert a small effect on the bond length. However, it is small, being less

than other variations considered in this paper and less than variations with other groupings of bonding electrons.

It should perhaps be pointed out that, in all the states considered in Tables 1 and 2 in which the grouping $(\sigma_1^2\sigma_2)$ exists, there is also present at least one electron in the σ_3 orbital; and moreover that, if only one electron is present in the σ_3 orbital, the resultant spin of the group of four electrons is zero. So, for all states examined one electron in the σ_1 orbital has its spin parallel to that of the electron in the σ_2 orbital, while the other has the same spin as the electron in the σ_3 orbital.

It follows from the above that the other σ_g orbital (σ_3) is then constructed from hybrids more concentrated in the bond region. No state has been considered in this paper in which there is an electron in the high-energy σ_u (or σ_4) orbital.

On the basis of the above, the ground states of N_2 and CO are ordinary triple bonds, there being three electrons of each spin concentrated in the bond region, each set of three having a similar configuration. However, the ground state of O_2, on this interpretation, is to be regarded as involving a distribution of electrons such that those of one spin form half a triple bond $(\sigma\pi^2)$, while those of the other spin form half a single (σ) bond. The distribution of electrons in the configuration of maximum probability can be described in the following way. Seven electrons of one spin are arranged at the corners of two tetrahedra with a common apex between the nuclei which are located inside the two tetrahedra; five electrons of the other spin are at the corners of two tetrahedra with a common base between the nuclei which are located inside the two tetrahedra. There are therefore four electrons between the two nuclei.

The first and the second excited state of O_2 involve the more normal double $(\sigma\pi)$ bonds. The difference between these two states has already been considered. All three states involve a concentration of four electrons in the bond region, and their equilibrium bond lengths are very nearly the same. The reason why the configuration involved in the $^3\Sigma_g^-$ state leads to the lowest energy is possibly that, in this state, the electrons concentrated in the bond region (and also the lone electrons) are, by the effect of the Pauli principle, separated spatially in the configuration of maximum probability so that the mean inter-electronic repulsion energy is less than for the other two states. The description of the binding in the ground state of O_2 as resulting from one single bond and two three-electron bonds is very close to the above if it is realised that the group of three electrons in a three-electron bond is distributed so that one electron (of one spin) has a high probability of being in the bond region while the other two (of the opposite spin) have a high probability of being on the two atoms, being " forced " out of the bond region because two electrons of the same spin tend to separate widely from one another. The present treatment therefore provides a bridge between the molecular-orbital and valence-bond descriptions.

Odd-electron Molecules.—The ground state of NO (and of O_2^+) has the electron distribution represented by $sp^3(\sigma\pi^2);sp^3(\sigma\pi)$ so that each atom is surrounded by a quartet of electrons of each spin but those of one spin contribute half a triple bond while those of the other contribute half a double bond, there being, in all, five electrons in the bond region. It is interesting to consider the dimerisation of NO on the present basis. One NO molecule involves three lone electrons on each atom and five in the bond region. If the dimer is to be produced it must be O=N–N=O. This structure involves twelve unshared electrons and ten shared electrons, which is the same as for two NO molecules. So, if there is any lowering of energy on dimerisation it is likely to be small. Though NO has an odd electron it cannot be said to have a free valency because, if an extra electron is brought on to the nitrogen (as must happen if the nitrogen is to form a two-electron covalent bond to another atom) the extra electron must be of such spin as to make two electron pairs on the nitrogen atom which are unshared with the oxygen atom, and thus the additional electron must have the same spin as the group of three in the bond region. Therefore, because in the first short period five electrons of parallel spin have a very low probability of being near one atom simultaneously, the addition of this extra electron must force one electron out of the NO bond region (in ONNO this would happen for both NO bonds). Therefore, the formation of the additional N–N bond must lead to a weakening of the two NO bonds from $2\frac{1}{2}$-bonds to double bonds. There can therefore be little lowering of energy on association

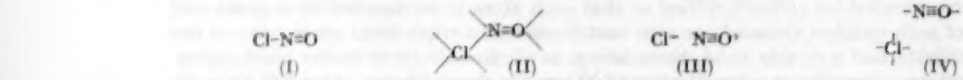
to counter the increase of entropy resulting from dissociation. The situation bears no resemblance at all to the association of halogen atoms or of free radicals like methyl which also contain an odd number of electrons.

But why is NO so stable compared with other possible diatomic odd-electron molecules involving elements of the first short period? The molecule CN is also formed from elements in adjacent groups of the Periodic Table; but it readily dimerises at ordinary temperatures to NCCN which has, in all, seven bonds. For there to be no increase in the total number of bonding electrons on association (this being the case for NO) the bond in CN would have to involve seven electrons. That is, four electrons of the same spin would have to be in the bond region. This is impossible because four valency shell electrons near an atom of the first short period must tend to distribute themselves tetrahedrally round the atom if they have the same spin. Consequently, there cannot be more than three electrons of the same spin serving to bind one atom to another. Hence the association of two CN molecules must lead to an increase in the number of bonding electrons and therefore association is much favoured energetically, and resembles the combination of halogen atoms and methyl radicals.

The molecule FO would also have an odd number of electrons and might resemble NO in existing as a monomer. However, the dimer F_2O_2 undergoes thermal decomposition at temperatures little greater than $-100°$ to O_2 and F_2. Nitric oxide is also unstable at room temperature with respect to N_2 and O_2, but the conversion involves a high energy of activation possibly because the change necessitates a considerable rearrangement of the electrons. The oxide KO_2 contains a paramagnetic ion O_2^- which contains 17 electrons (as would OF). It is tentatively suggested that this ion possesses stability with respect to dimerisation, analogous to that of NO, because on association two bonds involving three electrons in the bond region would be converted into three two-electron bonds. For this reason the association of this ion to O_4^{2-} would be expected to bear more resemblance to that of NO than to that of CN.

The low tendency of NO_2 and ClO_2 to dimerise may be accounted for in the same terms as for NO.

In the nitrosyl halides, XNO, the X–N bond lengths are much greater than the normal single-bond lengths while the N–O bond has approximately the same length (1·12 Å) as in nitric oxide (Ketelaar and Palmer, *J. Amer. Chem. Soc.*, 1937, **59**, 2629). This suggests that the N–O bond remains a five-electron bond while the X–N bond is weaker than a two-electron bond. Pauling (*loc. cit.*) accounted for this by suggesting that the electronic structure could be described best in terms of resonance between, *e.g.*, Cl–N=O and Cl^- $N{\equiv}O^+$. By analogy with the conclusions of this paper for diatomic molecules, the system may alternatively be described by supposing that the nine electrons of one spin have a configuration which may be represented by the first of Pauling's resonance structures (I) or (II),



each line in (II) representing one electron, while the nine of the other spin have a configuration corresponding to the second, (III) or (IV). On this basis, the complete wave function would be formulated so that the electrons of one spin occupied different orbitals from those of the other. The wave function would therefore differ from that corresponding to the resonance description. On the basis of this single structure the NO and NCl bonds are five-electron and one-electron bonds respectively. Similarly the nitrosyl compounds of the metals [*e.g.*, $Fe(CO)_2(NO)_2$] may perhaps have structures in which the NO retains its five-electron bond, the three electrons on the nitrogen all being shared with the metal atom. According to this description, the electrons of one spin would again occupy a different set of orbitals from those of the other spin.

It will be noted that the electronic structure ascribed in Table 2 to the ground state of CO^+ is not the same as that ascribed in Table 1 to the ground state of the isoelectronic N_2^+. In fact, the structures of the ground and excited $^2\Sigma$ states have been reversed for the two molecular ions. This has been done on the basis of the observed bond lengths and force

constants, and would appear to be justified by the way in which the data for these states then fall into line with the values for the other molecules as summarised in the graphs of Figs. 1—6. The electron in the σ_2 non-bonding orbital of CO^+ (ground state) has presumably a greater probability of being near the oxygen than near the carbon atom because of the higher nuclear charge of the former. Therefore, it would appear that the difference between the changes in bond length and vibration frequency ceased by the ionisation of N_2 and CO (originally stressed by Long and Walsh, *Trans. Faraday Soc.*, 1947, **43**, 342) is a consequence of the fact that with N_2 one of the bonding electrons is lost, leaving a five-electron bond which is only a little weaker than the six-electron bond of N_2 (for a $\sigma^2\pi^4$ bond is replaced by a $\sigma\pi^4$ bond), whereas with CO a non-bonding electron is lost and this is probably one mainly associated with the carbon atom since that has a lower nuclear charge. The small increase in binding is then probably a consequence of the increase in the effective nuclear charge of the carbon atom.

Conclusion.—It has been shown by using a description that employs simultaneously atomic and molecular orbitals, that the relative bond lengths and force constants for various states of the nine known diatomic molecules and ions derived from C, N, and O are, to a good approximation, related solely to the number of bonding electrons and to their distribution between σ and π bonding orbitals.

The spatial configuration of maximum probability of the electrons in these diatomic molecules has been considered on the same basis. In many excited states, and in some ground states, the configurations for the electrons of opposed spins are different from one another. Some consequences of this have been discussed.

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60. *The Effect of α-Chloro-substituents on the S_N1 Reactivity of the* C—Cl *Linkage.*

By B. BENSLEY and G. KOHNSTAM.

Kinetic study of the solvolysis of benzylidene chloride and benzotrichloride in aqueous acetone and ethanol, and of the ethanolysis of chloro- and dichloro-diphenylmethane, shows that replacement of an α-hydrogen atom by chlorine accelerates the ionisation of C–Cl linkages by reducing the activation energy, E. This is consistent with the view that, relatively to hydrogen, the additional chlorine atom acts as an electron donor in the transition state.[1]

The activation energy was temperature-dependent in the solvolysis of benzylidene chloride and its α-chloro-derivative, dE/dT being negative. This indicates a decrease in heat capacity on passage from the initial to the transition state, probably owing to increase in solvation associated with the development of electric charge. Similar behaviour is to be expected in all reactions having a transition state which is more polar than the initial state.

The effect of changes in the solvent on the rate, energy, and entropy of activation is consistent with the assumption that, for a given C–Cl separation, α-chlorination impedes the solvation of the incipient ions by ethanol molecules to a greater extent than it impedes solvation by water.

THERE is now considerable evidence [2] that the replacement of an α-hydrogen atom by chlorine accelerates the solvolysis of the C–Cl linkage when the reaction occurs by the ionisation mechanism, S_N1. The effect of such a substitution on the energy (E) and entropy of activation ($\Delta S^{\ddagger}$) is however not clear. An examination of the hydrolysis of

[1] Cf. Hughes, *Trans. Faraday Soc.*, 1941, **37**, 603.

[2] (*a*) Olivier and Weber, *Rec. Trav. chim.*, 1934, **53**, 869; (*b*) Evans and Hamann, *Trans. Faraday Soc.*, 1951, **47**, 25; (*c*) Hine and Lee, *J. Amer. Chem. Soc.*, 1951, **73**, 22; (*d*) Andrews and Kaeding, *ibid.*, p. 1007; (*e*) Vernon, *J.*, 1954, 423.

benzylidene chloride and benzotrichloride in aqueous acetone showed that α-chlorination accelerates ionisation by reducing E, $\Delta S^{\ddagger}$ being virtually unchanged.[2c] A study of the same compounds in aqueous ethanol, however, showed that this acceleration is due to an increase in $\Delta S^{\ddagger}$, E being also increased.[2b] In a recent investigation of the ionisation of allyl chloride in slightly aqueous formic acid, the increased reactivity of the α-chloro-derivative is seen [2e] to be due as much to a reduction of E as to a rise in $\Delta S^{\ddagger}$.

The present paper reports a kinetic investigation of the solvolysis of benzylidene chloride and benzotrichloride in aqueous acetone and ethanol. The reactions were studied at a number of different temperatures, as there was reason to suppose that E is not constant when the transition state is more polar than the initial reactant, and it was thought that this might account for the lack of concordance between the earlier results. The ethanolysis of chloro- and dichloro-diphenylmethane was also examined, though in less detail.

Experimental

Materials.—Commercial benzylidene chloride and benzotrichloride were dried ($CaCl_2$). Chlorodiphenylmethane was prepared by the method of Hughes, Ingold, and Taher,[3] and diphenyldichloromethane by that of Gattermann and Schultz.[4] All the organic chlorides were purified by distillation *in vacuo*, large head and tail fractions being discarded: Ph·$CHCl_2$, Ph·CCl_3, Ph_2CHCl, and Ph_2CCl_2, had n_D^{23} 1·5500, 1·5574, 1·5938, and 1·6034, respectively; the hydrolysable chloride was always within 99·6—99·8% of the theoretical amount.

Acetone was purified by Conant and Kirner's method [5] followed by fractionation through a 15-plate column; and ethanol by Manske's method [6] with precautions against the entrance of atmospheric moisture. An "x%" solvent was prepared by the addition of x ml. of the pure solvent to $100 - x$ ml. of water at room temperature.

Rate Measurements.—The thermostats were of conventional design, except that a well-stirred bath of melting ice was used for 0°. The temperatures, which were constant within ±0·01°, were measured with thermometers, standardised by the National Physical Laboratory to ±0·02°.

For the runs at the higher temperatures the reaction mixture was made up at 0°, and 3·76-ml. samples were pipetted into glass tubes which were sealed off and introduced, with vigorous shaking, into the thermostat in such quantities that the temperature regained its value within 2 min. Tubes were withdrawn from time to time, cooled rapidly to −80°, cleaned, broken under 200 ml. of cold, neutral acetone, and titrated with standard sodium hydroxide with lacmoid as indicator. For each batch of tubes, the zero reading was taken after 2—3 min., all the tubes having by then reached the thermostat temperature.

At the lower temperatures the reactant was added to the solvent in the thermostat, and 5-ml. samples were withdrawn from time to time, run into 200 ml. of cold, neutral acetone, and titrated as before. For the runs in absolute ethanol, it was desirable to prevent the entrance of moisture during sampling. The pipette was therefore attached to the flask through a ground-glass joint and fitted with a three-way tap, guard-tubes preventing the absorption of moisture.

Approximately the following initial concentrations were employed: Ph·$CHCl_2$, 0·008M; Ph·CCl_3, 0·005M; Ph_2CHCl, 0·012M; Ph_2CCl_2, 0·006M. The exact value of the initial concentration was usually obtained from an "infinity reading" which was always carried out in duplicate.

Integrated first-order rate coefficients were calculated from the equation $k_1 t = \ln [a/(a - x)]$, where the symbols have their usual meaning. In any one run, k_1 was generally obtained as the mean of ten separate determinations. At least two runs were always carried out for any given set of experimental conditions; if the two mean rate coefficients differed by more than ½% a further run was done.

The solvolysis of benzylidene chloride and benzotrichloride was studied in "50%" acetone, and "80%" and "50%" ethanol; that of chlorodiphenylmethane and its α-chloro-derivative in absolute ethanol. Several batches of each aqueous solvent were used, and each batch was monitored by examining the rate of solvolysis of a reactant which had already been studied in the previous batch. Any necessary correction was applied to the results.

The experimental data for two typical runs are given on p. 289: t in sec., k_1 in sec.$^{-1}$.

[3] Hughes, Ingold, and Taher, *J.*, 1940, 949.
[4] Gattermann and Schultz, *Ber.*, 1896, **29**, 2944.
[5] Conant and Kirner, *J. Amer. Chem. Soc.*, 1924, **46**, 232.
[6] Manske, *ibid.*, 1931, **53**, 1104.

(i) Benzotrichloride in " 50% " aqueous acetone at 30·05°; 5 ml. of reaction mixture titrated with 0·006427N-NaOH.

$10^{-3}t$	0	0·900	1·620	2·340	3·055	3·955	5·165	6·435	7·740	9·120	10·500	∞
Titre (ml.)	0·44	2·13	3·28	4·26	5·13	6·05	7·13	7·96	8·73	9·27	9·76	11·34
10^4k_1	—	1·871	1·864	1·844	1·842	1·827	1·842	1·820	1·847	1·821	1·852	—

10^4k_1 (mean) = 1·843; a duplicate run gave 1·850.

(ii) Dichlorodiphenylmethane in absolute ethanol at 0·00°; 4·11 ml. of reaction mixture titrated with 0·004933N-NaOH.

$10^{-3}t$	0	3·66	7·98	14·58	16·02	18·84	21·96	24·55	28·62	31·62	35·04	37·50	∞
Titre (ml.)	0·16	1·32	2·49	4·02	4·31	4·81	5·38	5·76	6·35	6·72	7·13	7·38	10·54
10^4k_1	—	(3·241)	3·186	3·192	3·187	3·153	3·184	3·159	3·170	3·162	3·176	3·172	—

10^4k_1 (mean) = 3·174; a duplicate run gave 3·164.

The solvolytic rates are summarised in Table 1, where the specific rates per replaceable chlorine atom, k, are quoted; they were obtained from the integrated rate coefficients by dividing by the number of chlorine atoms in the reactant molecule. The figures in each column refer to the same solvent, and each represents the mean of the results from, at least, two runs.

TABLE 1. *Specific rates* (10^5k, *in sec.*$^{-1}$) *per replaceable chlorine atom.*

" 50% " Aqueous acetone			" 50% " Aqueous ethanol			" 80% " Aqueous ethanol		
Temp.	$Ph{\cdot}CHCl_2$	$Ph{\cdot}CCl_3$	Temp.	$Ph{\cdot}CHCl_2$	$Ph{\cdot}CCl_3$	Temp.	$Ph{\cdot}CHCl_2$	$Ph{\cdot}CCl_3$
0·00°	—	1·359	0·00°	—	2·348	25·02°	—	1·633
9·94	—	5·380	10·08	—	10·80	35·00	—	5·550
20·00	—	19·14	20·04	1·802	42·77	45·01	—	19·32
30·05	1·830	61·53	30·00	7·040	146·6	50·00	2·489 [b]	34·43 [b]
39·92	6·225	174·4	39·99	24·64	454·0 [a]	54·96	—	54·00
50·04	19·88	—	49·99	77·75	—	60·13	7·785 [b]	99·47 [b]
60·04	57·20	—	60·07	223·9	—	64·81	—	155·0
69·74	149·4	—						
80·08	389·9	—						

[a] At 40·04°. [b] A different solvent which was not monitored.

Absolute ethanol		
Temp.	Ph_2CHCl	Ph_2CCl_2
0·00°	1·732	15·85
19·97	28·20	209·2

The rate coefficients were virtually independent of the initial concentration of the organic chloride. An increase in this quantity of a factor of 2 decreased k by 1% for $Ph{\cdot}CHCl_2$, and by 2·5% for $Ph{\cdot}CCl_3$.

Energies, Entropies, and Heat Capacities of Activation.—The activation energy, E, was calculated from the equation

$$E = [RT_aT_b/(T_b - T_a)] \ln k_b/k_a \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (i)$$

where k_a and k_b are the specific rates at the absolute temperatures T_a and T_b, respectively. E was not independent of T_a and T_b and was always found to obey the relation

$$E = E_0 + c(T_a + T_b)/2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (ii)$$

where E_0 and c are constants. The " best " values of E_0 and c, obtained by the method of least squares, are given in Table 2 for those cases in which the rate of solvolysis was examined at more

TABLE 2. E_0 *and* c (*in cal.*) *for the solvolysis of* $Ph{\cdot}CHCl_2$ *and* $Ph{\cdot}CCl_3$.

Solvent	" 50% " Acetone		" 50% " Ethanol		" 80% " Ethanol
Reactant	$Ph{\cdot}CHCl_2$	$Ph{\cdot}CCl_3$	$Ph{\cdot}CHCl_2$	$Ph{\cdot}CCl_3$	$Ph{\cdot}CCl_3$
$10^{-3}E_0$	31·63	33·53	41·20	43·13	35·94
c	-27 ± 3	-44 ± 4	-57 ± 3	-71 ± 6	-41 ± 2

than two temperatures. The standard deviation of c is also quoted. The agreement between the values of E calculated by these two equations is illustrated below for the solvolysis of benzotrichloride in " 80% " ethanol.

T_a (°K)	298·18	308·16	318·17	328·12
T_b (°K)	308·16	318·17	328·12	337·97
$10^{-3}E$ (cal.), from eqn. (i)	23·47	23·16	22·69	22·26
$10^{-3}E$ (cal.), from eqn. (ii)	23·51	23·10	22·69	22·29

The temperature-dependence of E, as calculated by means of equation (i), makes it necessary to establish the temperature to which this parameter refers. Strictly, the activation energy is defined by the differential equation $E = \boldsymbol{R}T^2(\mathrm{d} \ln k/\mathrm{d}T)$. If E is a linear function of temperature in the range T_a to T_b, and $(\mathrm{d}E/\mathrm{d}T)(T_a - T_b)^2/(T_a + T_b) \ll E$, it can be shown that equation (i) gives E at $(T_a + T_b)/2$, the mean of the two temperatures employed. Equation (ii) then implies a linear E–T relation over the whole experimental range with $\mathrm{d}E/\mathrm{d}T = c$. The results in Table 2 show that, within the limits of experimental error, this equation applies to all the reactions listed [$c(T_a - T_b)^2/(T_a + T_b)$ is always very much less than E], and it was therefore assumed that all activation energies obtained from equation (i) referred to the mean of the two appropriate temperatures.

The heat capacity of activation, $\Delta C^\ddagger$, was calculated from the expression $\Delta C^\ddagger = \mathrm{d}E/\mathrm{d}T - \boldsymbol{R}$, which is readily derived from the relation between the energy and enthalpy of activation.[7a]

The entropy of activation, $\Delta S^\ddagger$, at the temperature $(T_a + T_b)/2$, was obtained from the expression

$$\ln h_a = \ln (\boldsymbol{k}/\boldsymbol{h}) + \ln (T_a + T_b)/2 + 1 + \Delta S^\ddagger/\boldsymbol{R} - E/\boldsymbol{R}T_a$$

where k_a refers to the temperature T_a, and E to $(T_a + T_b)/2$. This expression was derived from the conventional form of the absolute rate equation for reactions in solution [8] by assuming that $\Delta S^\ddagger$ varies with the temperature according to $\mathrm{d}(\Delta S^\ddagger)/\mathrm{d}T = \Delta C^\ddagger/T$. If E refers to the mean of the two temperatures employed in its calculation by equation (i), it can be shown that the above expression does in fact give $\Delta S^\ddagger$ at $(T_a + T_b)/2$.

Values of E, $\Delta S^\ddagger$, and $\Delta C^\ddagger$ are given in Table 3 for the reactions studied in this investigation. E and $\Delta S^\ddagger$ are quoted at temperatures which are within the experimental range, and common to the two reactants investigated in the same solvent. E and $\Delta C^\ddagger$ are the "least squares" values obtained from equation (ii) after substitution from equation (i). $\Delta S^\ddagger$ was always

TABLE 3. *Energies, entropies, and heat capacities of activation.*

Solvent	"50%" Acetone		"50%" Ethanol		"80%" Ethanol		Absolute ethanol	
Reactant	$Ph{\cdot}CHCl_2$	$Ph{\cdot}CCl_3$	$Ph{\cdot}CHCl_2$	$Ph{\cdot}CCl_3$	$Ph{\cdot}CHCl_2$	$Ph{\cdot}CCl_3$	$Ph_2{\cdot}CHCl$	$Ph_2{\cdot}CCl_2$
Temp.	35·00°	35·00°	35·00°	35·00°	55·06°	55·06°	9·99°	9·99°
E (kcal.)	23·31	19·97	23·63	21·24	24·11 [a]	22·43 [a]	22·23	20·56
$\Delta S^\ddagger$ (cal. °K^{-1})	− 9·97	−14·0	− 6·22	− 8·07	−11·8 [a]	−11·8 [a]	− 5·43	− 7·12
$\Delta C^\ddagger$ (cal. °K^{-1})	-29 ± 3	-46 ± 4	-59 ± 3	-73 ± 6	—	-43 ± 2	—	—

[a] A different solvent which was not monitored.

calculated from the specific rate per replaceable chlorine atom. Where $\Delta C^\ddagger$ has been determined, E and $\Delta S^\ddagger$ can be obtained at temperatures other than those given in Table 3, but such a procedure is only justified for temperatures which are not too far outside the experimental range, as there is no reason to suppose that $\Delta C^\ddagger$ has the same value at all temperatures.

DISCUSSION

The rate of reaction between hydroxylic solvents and compounds having more than one chlorine atom directly attached to the reaction centre is entirely controlled by the heterolysis of one of the C–Cl linkages, the subsequent stages taking place very rapidly.[9] Hydroxide ions do not accelerate the hydrolysis of benzylidene chloride and benzotrichloride,[2a] and ethoxide ions have no effect on the ethanolysis rate of dichlorodiphenylmethane.[2d] The rate-determining step in these reactions must therefore involve the unimolecular mechanism, S_N1;[1] the ethanolysis of chlorodiphenylmethane has also been shown to occur by this mechanism.[10] In the present investigation, all the reactions followed the first-order rate-law and large changes in the initial concentration had only a small effect on the rate. This shows that mass-law and ionic-strength effects [11] are not

[7] Glasstone, Laidler, and Eyring, "The Theory of Rate Processes," McGraw-Hill, New York, 1941, (*a*) p. 198; (*b*) p. 419—423.
[8] *Op. cit.*, p. 199.
[9] Cf. Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, 1953, p. 329.
[10] Bateman, Hughes, and Ingold, *J. Amer. Chem. Soc.*, 1938, **60**, 3080.
[11] Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 979.

operating to any significant extent, and it is therefore possible to identify the specific rate per replaceable chlorine atom with the specific rate of ionisation of one of the C–Cl linkages.

The Effect of α-Chlorination on the Rate.—The results given in Table 4 show that the replacement of an α-hydrogen atom by chlorine, in benzylidene chloride and chlorodiphenylmethane, accelerates the ionisation by reducing the activation energy. The accompanying changes in the entropy of activation are, relatively, much smaller and tend, in general, to retard ionisation.†

TABLE 4. *Effect of α-chlorination on the ionisation of the* C–Cl *linkage.*

(The subscripts H and Cl refer to a compound and its α-chloro-derivative, respectively.)

Solvent	"50%" Acetone	"50%" Ethanol	"80%" Ethanol	Ethanol
Reactant [a]	$Ph{\cdot}CHCl_2$	$Ph{\cdot}CHCl_2$	$Ph{\cdot}CHCl_2$	Ph_2CHCl
Temp.	30·05°	30·00°	55·06°	9·99°
k_{Cl}/k_H	33·65	20·75	13·1	8·31
$E_{Cl} - E_H$ (kcal.)	−3·26	−2·32	−1·68	−1·67
$\Delta S^*_{Cl} - \Delta S^*_H$ (cal. °K^{-1})	−3·83	−1·63	0·00	−1·69

[a] Only the compound containing the replaceable α-hydrogen atom is quoted.

Because of the temperature-dependence of E and ΔS^* (see Experimental section), it is necessary to compute changes in these quantities (resulting from α-chlorination) from data at the same temperature. If the figures for the α-chloro-derivative refer to a lower temperature than those for the parent compound, the negative heat capacity of activation (cf. Table 3) leads to apparent changes in these quantities which become increasingly more positive as the temperature difference is increased. This accounts for the slightly smaller changes in E and ΔS^* reported by Hine and Lee [2c] for the effect of α-chlorination on the rate of ionisation of benzylidene chloride in "50%" acetone. At the temperatures appropriate to their work,‡ our values of E and ΔS^* for the two compounds do not differ from theirs by more than 0·14 kcal. and 0·5 e.u., respectively. Similarly, the observation [2c] that the accelerating effect of α-chlorination on the ionisation of allyl chloride in slightly aqueous formic acid is as much due to an increase in ΔS^* as to a decrease in E is considered to arise out of the fact that the two compounds were examined at temperatures which differed by about 50°. It is pointed out in the following section that a negative heat capacity of activation is to be expected whenever the transition state is more polar than the initial state, and the assumption of a reasonable value for ΔC^* leads to the conclusion that a comparison of the two compounds at the same temperature can be expected to show that the increase in rate is almost completely, if not entirely, due to a reduction of E, as in the present investigation.

Our results in "80%" ethanol do not confirm those of Evans and Hamann [2b] who found that α-chlorination in benzylidene chloride accelerates the ionisation in this solvent by increasing ΔS^*; the accompanying change in E tended to retard the reaction. For the ionisation of one of the C–Cl linkages, their data actually lead to a slightly smaller increase in ΔS^* than reported ‖ but, a reasonable value being assumed for ΔC^* (cf. Table 3), this increase is still so large that it can be only partially accounted for by the fact that E and ΔS^* refer to a temperature which is 30° lower for the α-chloro-derivative than for the parent

† The magnitude of the changes in E and ΔS^*, resulting from α-chlorination, depends to some extent on the temperature under consideration, as ΔC^* is more negative for benzotrichloride than for benzylidene chloride (cf. Table 3). These changes therefore become more positive as lower temperatures are chosen. The choice of temperatures for this comparison is, however, restricted to those which are not too far outside the experimental range, as ΔC^* was determined from experimental data and is unlikely to have the same value at all temperatures. It can readily be verified that, within the limits imposed by these restrictions, the predominant cause of the acceleration of the ionisation is the reduction of E.

‡ E and ΔS^*, calculated from rate data at two temperatures, refer to the mean of these two temperatures (cf. Experimental section).

‖ At first sight, the rate constants reported by Evans and Hamann appear to refer to the ionisation of one of the C–Cl linkages. They were obtained from the "experimental" rate constants by dividing by n, the number of replaceable chlorine atoms in the reactant molecule, but the method employed for the calculation of the "experimental" constants can be shown to lead to values which are greater than rate constants for solvolysis by a factor of n. When $n > 1$, ΔS^* for the ionisation of one C–Cl linkage is thus smaller than ΔS^* reported by these authors. The difference is $R \ln n$; the value of E is the same.

compound. A comparison of their rates of ionisation with those of the present investigation in the same solvent, and at the same temperature, shows good agreement for the reaction of benzotrichloride but serious discrepancies when the reactant is benzylidene chloride; at, *e.g.*, 60° their rate of ionisation for this compound is almost twice as great as ours. Our observation that α-chlorination accelerates the ionisation in "80%" ethanol by reducing E is consistent with our findings in the other solvents employed, and our rates of ionisation for benzylidene chloride are in good agreement with those previously reported in "50%" acetone [2a, c] and "50%" ethanol.[12] The present results in "80%" ethanol are therefore regarded as the more reliable.

The results of this investigation are fully consistent with the predictions of Hughes [1] who suggested that the replacement of an α-hydrogen atom by chlorine accelerates the rate of ionisation of the C–Cl linkage by conjugatively releasing electrons towards the reaction centre, a process which increases the stabilisation of the transition state. In agreement with the present observations, and those of Hine and Lee,[2c] this requires that the acceleration results mainly from a reduction of E. The view that the additional chlorine atom increases the rate of ionisation by increasing steric hindrance to solvation in the transition state—the conclusion to be drawn from the work of Evans and Hamann [2b]—involves an appreciable increase in ΔS^* on α-chlorination and is, therefore, not supported by our results. An acceleration of the reaction arising out of a reduction of E would, however, also have been observed if the replacement of hydrogen by the larger chlorine atom decreases the stability of the initial state because of steric effects.[13] There is some steric compression between chlorine and the *o*-hydrogen atoms in benzotrichloride, though not in benzylidene chloride, but the non-bonding energy, calculated according to the methods of Dostrovsky, Hughes, and Ingold,[14] is only 110 cal. It has been suggested [15] that these methods underestimate the interatomic penetration energy but, even if it is assumed that chlorine and hydrogen atoms are as difficult to compress as two helium atoms, the substitution of Slater's data [16] in Buckingham's equation [17] does not increase the non-bonding energy beyond 800 cal. This is less than half the smallest observed decrease in E on α-chlorination (cf. Table 4), and it does not, therefore, seem likely that increased steric compression in the initial state of the α-chloro-derivative is mainly responsible for the present observations.

The Temperature Effect.—It has already been pointed out that the sovolysis of benzylidene chloride and benzotrichloride involves temperature-dependent activation energies, dE/dT being negative and constant within the limits of experimental error. These observations cannot be due to a composite chemical mechanism in the rate-determining stage—this requires positive dE/dT values—and it is therefore necessary to discuss them in more detail. On purely theoretical grounds several workers have stressed that E is not constant if the heat capacity of the activated complex differs appreciably from that of the initial reactants.[18] The conventional form of the absolute rate equation [8] leads to the same conclusion, with $dE/dT = \Delta C^* + \boldsymbol{R}$. Temperature-dependent values of E have been reported on a number of occasions though not all the claims to have observed this effect can be accepted; summaries of the earlier work are available,[19] and some of the more recent investigations in this field are discussed later in this section.

In the present reactions, the rate is determined by the ionisation of one of the C–Cl linkages, and the rate coefficients for this process, rather than for the overall solvolysis, have been quoted throughout this paper. It is an essential feature of reaction by this mechanism that the activation energy is reduced to accessible values by the solvation of the

[13] Andrews and Linden, *J. Amer. Chem. Soc.*, 1947, **69**, 2091.
[13] Cf. Brown *et al.*, *ibid.*, 1949, **71**, 1845; 1950, **72**, 5068; Hughes, Ingold, Martin, and Meigh, *Nature*, 1950, **166**, 679.
[14] Dostrovsky, Hughes, and Ingold, *J.*, 1946, 173.
[15] Westheimer, *J. Chem. Phys.*, 1947, **15**, 252.
[16] Slater, *Phys Rev.*, 1928, **32**, 349.
[17] Buckingham, *Proc. Roy. Soc.*, 1938, *A*, **168**, 264.
[18] Trautz, *Z. anorg. Chem.*, 1918, **102**, 81; Brandsma and Scheffer, *Rec. Trav. chim.*, 1926, **45**, 522; La Mer, *J. Chem. Phys.*, 1933, **1**, 289.
[19] (*a*) Kohnstam, Thesis, London, 1948; (*b*) Moelwyn-Hughes, "Kinetics of Reactions in Solution," Clarendon Press, Oxford, 1947, chap. 2; La Mer and Miller, *J. Amer. Chem. Soc.*, 1935, **57**, 2664.

transition state,[20] and it is generally accepted that this process requires a definite orientation of the solvent dipoles around the incipient ions. These oriented molecules are less free to move than those in the bulk of the solvent and can therefore be expected to have a lower entropy and heat capacity. Analogous considerations apply to fully developed ions in solution, and this " freezing-out " of solvent molecules in the immediate neighbourhood of charged particles has been stated to account for the negative partial molar heat capacities of electrolytes [21] and the negative heat capacity of ionisation of weak acids.[22] Similarly, reactions which involve an increase in electric charge, and hence in solvation, on passing into the transition state should show negative ΔC^* values; [23] Moelwyn-Hughes [24] also regards this as one possible explanation of the negative temperature coefficient of E, observed in the hydrolysis of methyl fluoride.

Negative ΔC^* values have also been observed for a few other reactions in which the transition state is more polar than the initial reactants. In the hydrolysis of acetic anhydride in water and aqueous acetone ΔC^* varies between −85 and −55 cal. depending on the solvent composition; [25] its value is about −60 for the solvolysis of 1-methylallyl chloride in " 50% " aqueous ethanol,[26] about −40 for the hydrolysis of diphenylchloromethane in aqueous acetone,[27] −45 for the hydrolysis of methyl nitrate in water,[28] and about −70 for the same reaction of the methyl halides,[29] though in a later investigation over the same temperature range ΔC^* was found to increase with increasing temperature, finally attaining positive values.[30] In view of the number of reactions of this type which have been investigated it is perhaps surprising that more examples are not available. On the other hand, the use of small temperature ranges and some inaccuracy in the rates—E values are often quoted as accurate to ±0·5 kcal.—may have prevented the observation of this effect when ΔC^* is numerically small. The determination of E from the Arrhenius plot may also have obscured its temperature-dependence, but an examination of a number of previous investigations does not lead to any further, reliable examples. Thus, with the exception of the most recent work on the methyl halides, all the available evidence is consistent with the prediction that an increase of electric charge on passing over into the transition state reduces the heat capacity.

The same prediction, however, arises out of the electrostatic approach, based on the Born relation which treats the solvent as a continuous medium of dielectric constant D. This approach considers a contribution to E, E_D, due to electrostatic effects in a continuous dielectric. For all known solvents D decreases with increasing temperature, so that E_D, and hence E, can be expected to be temperature-dependent. In general, the electrostatic theory leads to good agreement with experimental observations. It has been employed in a discussion of the effect of D on the rates of bimolecular reactions between dipolar molecules and on the rate of ionisation of *tert.*-butyl chloride,[7b] in the calculation of the electrostatic contribution to ΔS^* in similar bimolecular processes [31] where there is an additional negative contribution to ΔS^* due to the combination of two reactant molecules to form a single activated complex, in the calculation of ΔH^* and ΔS^* for the ionisation of alkyl halides,[32] and in the discussion of a large number of ionic and ion-dipole reactions.[33]

In applying the electrostatic approach to the present problem, the ionisation of the

[20] Ref. 9, p. 312.
[21] Randall and Rossini, *J. Amer. Chem. Soc.*, 1928, **51**, 323.
[22] (*a*) Everett and Wynne-Jones, *Trans. Faraday Soc.*, 1939, **35**, 1380; (*b*) Coulson and Everett, *ibid.*, 1940, **36**, 663.
[23] Ingold, personal communication, see ref. 19*a*; Caldin, Long, and Trowse, *Nature*, 1953, **171**, 1124.
[24] Moelwyn-Hughes, *Proc. Roy. Soc.*, 1952, *A*, **211**, 254.
[25] Gold, *Trans. Faraday Soc.*, 1948, **44**, 506.
[26] Vernon, personal communication.
[27] Hughes, Ingold, and Kohnstam, unpublished work; cf. ref. 19*a*.
[28] McKinley-McKee and Moelwyn-Hughes, *Trans. Faraday Soc.*, 1952, **48**, 246.
[29] Moelwyn-Hughes, *Proc. Roy. Soc.*, 1938, *A*, **164**, 295; ref. 24.
[30] *Idem, ibid.*, 1953, *A*, **220**, 386.
[31] Pearson, *J. Chem. Phys.*, 1952, **20**, 1478.
[32] Franklin, *Trans. Faraday Soc.*, 1952, **48**, 443.
[33] For summary, see Amis, " Kinetics of Chemical Change in Solution," Macmillan, New York, 1949, chap. 4—6, 8, 9.

C–Cl linkage, the electrostatic contribution to ΔS^* is obtained by differentiating Kirkwood's equation [34] with respect to temperature: [31] †

$$\Delta S_D = \left\{\frac{\mu_f^2}{r_f^3} - \frac{\mu_i^2}{r_i^3}\right\} \cdot \frac{3D}{(2D+1)^2} \cdot \frac{\mathrm{d} \ln D}{\mathrm{d}T}$$

where μ and r are the dipole moment and molecular radius, and the subscripts i and f refer to the initial and the transition state, respectively. The electrostatic contribution to ΔC^* is then given by:

$$\Delta C_D = \left\{\frac{\mu_f^2}{r_f^3} - \frac{\mu_i^2}{r_i^3}\right\} \cdot \frac{3DT(2D-1)}{(2D+1)^3} \cdot \left\{\frac{\mathrm{d} \ln D}{\mathrm{d}T}\right\}^2$$

as $(\mathrm{d} \ln D/\mathrm{d}T)$ is independent of T for our solvents.[35]

Our experimental values for ΔS^* and ΔC^* at 55° are compared in Table 5 with those calculated for ΔS_D and ΔC_D, it being assumed that $(\mu_f^2/r_f^3 - \mu_i^2/r_i^3)$ is 82 kcal. It is to be expected that the stretching of the C–Cl bond in the transition state results in a positive contribution to ΔS^*, but this is unlikely to be greater than 2—3 cal. ΔC_D should be identical with ΔC^*.

TABLE 5. *Electrostatic and experimental entropies and heat capacities of activation (in cal. °K^{-1}) for the ionisation of the* C–Cl *linkage at* 55°.

Solvent	" 50% " Acetone	" 50% " Ethanol	" 80% " Ethanol
D [a]	45	45	27
10^3 (d ln D/dT) [a]	− 5·4	−5·4	− 6·1
ΔS_D	− 7·24	−7·24	−12·5
ΔS^* Ph·CHCl$_2$	−11·8	− 9·9	−11·8
ΔS^* Ph·CCl$_3$	−16·8	−12·7	−11·8
ΔC_D	−12·5	−12·5	−23·7
ΔC^* Ph·CHCl$_2$	−29	−59	—
ΔC^* Ph·CCl$_3$	−46	−73	−43

[a] Akerlof, ref. 35.

The figures in Table 5 show that the predictions of the theory are not supported by our observations. This might be thought to be due to the choice of an inappropriate value for $(\mu_f^2/r_f^3 - \mu_i^2/r_i^3)$ which may vary from solvent to solvent. A change of solvent should, however, affect ΔS^* and ΔC^* in the same manner irrespective of the value of this term and it can be seen that both compounds show an *increase* in ΔS^* and an appreciable *decrease* in ΔC^* on going from " 50% " acetone to " 50% " ethanol. It is also noteworthy that, even if this term is chosen so that ΔS_D is 3 cal. less than ΔS^*, ΔC_D is usually much less than ΔC^*.‡ This conclusion is analogous to previous findings that temperature-dependent E values are not generally associated with constant isodielectric activation energies ‖ as required by the theory,[25,36] though this requirement is occasionally obeyed.[37] Similarly, it has already been reported [22a] that the Born relation only accounts for part of the heat capacity of ionisation of weak acids.

† Kirkwood's equation gives the free energy of a dipole in a medium of dielectric constant D relative to its value in a vacuum. Differentiation with respect to temperature gives its entropy relative to the same reference state, but this quantity is equal to ΔS_D as electrostatic entropy effects are zero when the dielectric constant of the medium is independent of temperature.

‡ *Added in Proof.*—Enthalpies and entropies of activation derived from Kirkwood's equation have recently been compared with the experimental values for a number of bimolecular reactions which involve an increase in polarity on passage into the transition state (Caldin and Peacock, *Trans. Faraday Soc.*, 1955, **51**, 1217). Here too the predictions of the theory are not confirmed by the experimental observations.

‖ Determined by varying the solvent composition in such a way that D is independent of the temperature.

[34] Kirkwood, *J. Chem. Phys.*, 1934, **2**, 351.
[35] Akerlof, *J. Amer. Chem. Soc.*, 1932, **54**, 4125.
[36] Amis *et al.*, *J. Phys. Chem.*, 1943, **47**, 338; *J. Amer. Chem. Soc.*, 1941, **63**, 2231, 2621, 2883; also ref. 25.
[37] Amis and La Mer, *J. Amer. Chem. Soc.*, 1939, **61**, 905; Winstrom and Warner, *ibid.*, p. 1205.

It is also noteworthy that the ionisation of triphenylmethyl chlorides and the rate of ionisation of *tert.*-butyl chloride, in widely different solvents, does not vary with D in the expected manner.[38] These, and other deviations from the behaviour predicted for a continuous dielectric,[33, 76] are now regarded as due to specific solvent effects. The Born relation accounts well for the long-range forces between charged particles in solution but is only applicable beyond the first solvation shell.[22b, 39]

The considerations outlined in the preceding paragraphs lead to the conclusion that the temperature-dependence of E, observed in ionisation reactions, arises out of the operation of specific solvation forces in the transition state. On this view, the magnitude of ΔC^* for the ionisation of molecules of similar size in the same solvent can be regarded as a measure of the increase in the extent of solvation on passing into the transition state. The results in Table 5 then indicate that this solvation is greater for benzotrichloride than for benzylidene chloride in both " 50% " acetone and " 50% " ethanol, and this conclusion is supported by the values of ΔS^* for these reactions. Although a small positive contribution to ΔS^* is to be expected, arising out of the bond stretching in the transition state, increased solvation should decrease ΔS^*, as observed. Our results do not permit a discussion of the dependence of the extent of this solvation on the nature of the solvent; acetone is a poor solvating medium, but both constituents are involved in the ethanolic solvents. It does, however, seem likely that the appreciable increase in ΔC^* on going from " 50% " to " 80% " ethanol is not entirely due to a decrease in solvation, as the excess heat capacity of mixing is considerably larger in the more aqueous solvent.[40]

Our values for ΔC^* in aqueous acetone refer to an incomplete ionisation, but are much the same as the partial molar heat capacity of hydrochloric acid in water,[41] and the heat capacity of ionisation of weak acids in the same solvent.[22a] It may be that the extent of solvation in the transition state is not unduly different from that of fully developed ions, and the known variation of partial molar heat capacities with cationic size [21] could also be responsible for part of these observations. It may also be that the partial molar heat capacity of water is greater in aqueous acetone than when it is pure, but this view is not supported by the decrease of ΔC^* with increasing water content, observed in the hydrolysis of acetic anhydride in aqueous acetone.[25] It has recently been suggested [30] that the transition state for the hydrolysis of methyl halides has zero heat capacity, and that, therefore, ΔC^* is numerically equal to the partial molar heat capacity of the initial reactant. In our reactions, it is difficult to accept a scheme which does not envisage the participation of additional solvent molecules in the activated complex, but it is possible that part of the loss of heat capacity on passing into the transition state arises out of a reduction in the heat capacity of the organic chloride. At present there is not sufficient information available to allow us to decide why our values for ΔC^* are so close to the corresponding values when ionisation is complete.

The Solvent Effect.—The results given in Table 4 show that the acceleration of the ionisation of the C–Cl linkage, caused by α-chlorination in benzylidene chloride, decreases along the solvent series " 50% " acetone > " 50% " ethanol > " 80% " ethanol. The corresponding changes in E and ΔS^* increase in the same order. This is illustrated below for the reaction at 55°; the subscript $_H$ refers to benzylidene chloride, $_{Cl}$ to benzotrichloride.

Solvent	" 50% " Acetone	" 50% " Ethanol	" 80% " Ethanol
$E_{Cl} - E_H$ (kcal.)	−3·69	−2·65	−1·67
$\Delta S^*_{Cl} - \Delta S^*_H$ (cal. °K^{-1}) ...	−5·0	−2·9	0·0

The transition state of ionisation of benzotrichloride is more heavily solvated than that of benzylidene chloride (see preceding section), and it might be thought that a decreasing capacity for solvating such transition states is responsible for our observations. This,

[38] Brown and Hudson, *J.*, 1953, 3352; Evans, Price, and Thomas, *Trans. Faraday Soc.*, 1955, **51**, 481.
[39] Eley and Evans, *ibid.*, 1938, **34**, 1093.
[40] Prigogine and Defay, "Chemical Thermodynamics," Longmans Green and Co., London, 1954, p. 431.
[41] Ramage and Randall, *J. Amer. Chem. Soc.*, 1927, **49**, 92.

however, requires an increase in E along the solvent series, while it is found that, in the ionisation of benzylidene chloride, E is unaltered by changing from "50%" acetone to "50%" ethanol at 35° and is actually reduced a little when the change at 55° is considered (cf. Table 3).

Our findings are consistent with the view that, for a given C–Cl separation, the replacement of an α-hydrogen atom by the larger chlorine results in increased steric hindrance to the solvation of the incipient ions. Any steric opposition to the approach of solvent molecules will be greater for the bulkier ethanol molecules than for water, and if this impedance of solvation is enhanced by α-chlorination, $E_{Cl} - E_H$ should increase with increasing participation of ethanol in the solvation process. This participation increases along our solvent series. The same explanation accounts for the observation that $E_{Cl} - E_H$ is −1·67 kcal. for the ionisation of chloro- and dichloro-diphenylmethane in absolute ethanol at 10° (cf. Table 4), and not greater than −3 kcal. in "85%" acetone at 12·5°.[42] The observation that $\Delta S^*_{Cl} - \Delta S^*_H$ increases along this solvent series is also consistent with this view. It is, however, worth noting that the overall effect of increased steric hindrance to solvation is a retardation of the ionisation process.

The assumption that α-chlorination enhances steric effects of this type is not inconsistent with our earlier conclusion that it also leads to increased solvation in the transition state of ionisation. This state corresponds to that C–Cl separation for which the energy is a maximum, and two different contributions to this energy may be considered; one is the same as when the ionisation occurs in the gaseous phase, the other arises out of the solvation forces. Both increase with increasing charge development and bond extension. Relative to hydrogen, the additional chlorine atom in the α-chloro-derivative releases electrons towards the reaction centre and thus permits an increased C–Cl separation without increasing the "gaseous" ionisation energy; the greater bond extension also favours solvation. It thus seems reasonable to suppose that the transition state of the α-chloro-derivative is associated with a greater C–Cl separation which is sufficient to outweigh any steric hindrance to solvation arising out of the replacement of hydrogen by the larger chlorine atom. On this view, α-chlorination should lead to a reduction of E, and increased solvation in the transition state, as observed. Even in the absence of such steric effects † it is difficult to visualise the same bond extension in the transition states of the two compounds, as then no factors which tend to favour increased solvation are apparent in the α-chloro-derivative.

In the ionisation of benzotrichloride, these arguments could be employed to justify the assumption that the increasing participation of ethanol in the solvation process results in increasing C–Cl separation in the transition state, such that the solvation energy is independent of the solvent composition. The increase in E along the solvent series, "50%" acetone, "50%" ethanol, "80%" ethanol, then arises out of an increase in the "gaseous" ionisation energy. This view, however, is not supported by the observed increase in $\Delta S^*_{Cl} - \Delta S^*_H$, which is regarded as too large to be solely due to increasing bond extension. It is therefore considered that these changes in solvent involve some decrease in the extent of solvation of the transition state.

We are indebted to Professors C. K. Ingold and E. D. Hughes for permission to quote unpublished work and for valuable comments, to Mr. C. A. Vernon for making some unpublished results available to us, to Imperial Chemical Industries Limited for the gift of benzylidene chloride, and to the Council of the Durham Colleges for the award of a Post-graduate Studentship (to B. B.).

University Science Laboratories,
South Road, Durham. [*Received, June 28th*, 1955.]

† Our results do not allow us to draw any conclusions regarding the operation of these effects in "50%" acetone, where only water is involved in the solvation process.

[42] Bensley and Kohnstam, *J.*, 1955, **3408**.

61. 16-*Oxo-* and 16α-*Hydroxy-testosterone.*

By (Mrs.) W. J. Adams, D. K. Patel, V. Petrow, and (Mrs.) I. A. Stuart-Webb.

An improved route to 16-oxotestosterone (IX; R = H) is described. Androst-5-ene-3β : 16α : 17β-triol (V; R = R′ = H), hitherto obtained only with difficulty, has been prepared by reduction of 3β : 16α-diacetoxyandrost-5-en-17-one. It has been converted into 16α-hydroxytestosterone (VI; R = H) by microbiological oxidation.

The compounds named in the title were required for biological study.

Preparation of 17β-acetoxyandrost-4-ene-3 : 16-dione (IX; R = Ac) by the methods of Stodola and Kendall [1a] and Butenandt, Schmidt-Thomé, Weiss, Dresler, and Meinerts [1b] proved unsatisfactory owing to low overall yield. We therefore developed an improved procedure from methyl 3β-acetoxy-16 : 17-*seco*androst-5-ene-16 : 17-dioate (I; R = Ac, R′ = Me).

3β-Hydroxy-16 : 17-*seco*androst-5-ene-16 : 17-dioic acid (I; R = R′ = H) was originally prepared by oxidation of cholesteryl acetate dibromide with chromic acid.[2] Its acetate (I; R = Ac, R′ = H) was later obtained by hypoiodite oxidation of 3β-acetoxyandrost-5-en-17-one.[3] An improved route to the hydroxy-ester (I; R = H, R′ = Me), for which we are indebted to Dr. B. Ellis of these Laboratories, lies in the chromic acid oxidation of 3β-acetoxy-5ξ : 6ξ-dibromopregn-16-en-20-one, followed by debromination of the product to give the acetate (I; R = Ac, R′ = H), which is then converted into the 16-monomethyl ester of the acid (I; R = H) with methanolic hydrogen chloride and thence into the required hydroxy-diester with diazomethane.

Methyl 3β-hydroxy-16 : 17-*seco*androst-5-ene-16 : 17-dioate (I; R = H, (R′ = Me) was oxidised to methyl 3-oxo-16 : 17-*seco*androst-5-ene-16 : 17-dioate (IV; R = CO_2Me) by aluminium *tert.*-butoxide–*cyclo*hexanone. The crude product (>90% yield) was converted into methyl 3 : 3-ethylenedioxy-16 : 17-*seco*androst-5-ene-16 : 17-dioate (VII; R = CO_2Me) by treating its solution in ethylene glycol with boron trofluoride–ether complex. Intramolecular acyloin condensation of this ester with sodium in liquid ammonia [4] led to the formation of 3 : 3-ethylenedioxy-17β-hydroxyandrost-5-en-16-one (VIII; R = H). Removal of the ethylenedioxy-residue and reacetylation furnished the required 17β-acetoxyandrost-4-ene-3 : 16-dione (IX; R = Ac). Its cautious hydrolysis with methanolic potassium hydrogen carbonate gave 16-oxotestosterone (IX; R = H), since described by Meyer and Lindberg.[5]

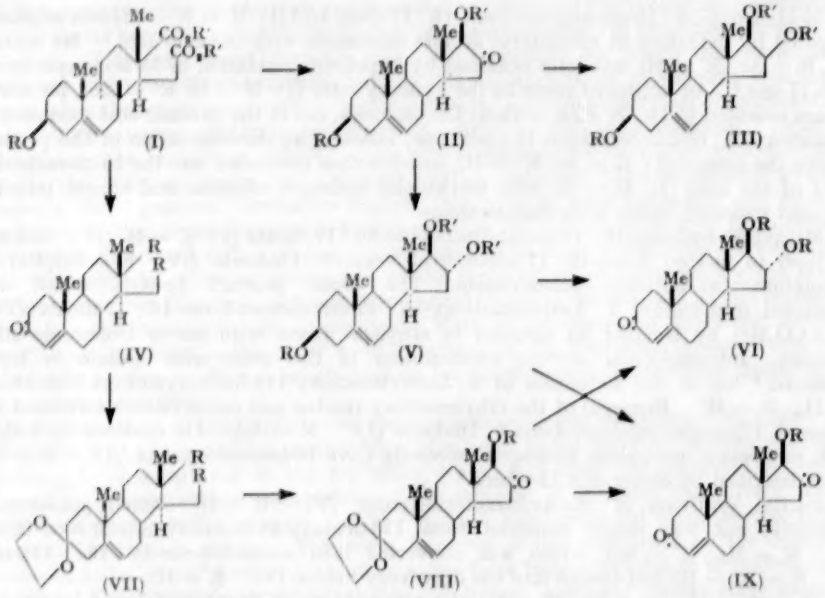
Partial synthesis of 16α-hydroxytestosterone (VI; R = H) offered considerable difficulty, but was finally achieved from 17β-acetoxy-3β-methoxyandrost-5-en-16-one (II; R = Me, R′ = Ac), which was converted into androst-5-ene-3β : 16α : 17β-triol (V; R = R′ = H) and thence into the dihydroxy-ketone (VI; R = H).

The ether (II; R = Me, R′ = H) was prepared by Huffman and Lott [6] by Stodola reduction [7] of 16-hydroxyimino-3β-methoxyandrost-5-en-17-one. An alternative route lies in the acyloin condensation of methyl 3β-methoxy-16 : 17-*seco*androst-5-ene-16 : 17-dioate with sodium in liquid ammonia [4] followed by acetylation of the product. The diacetate (II; R = R′ = Ac) may similarly be prepared from the ester acetate (I; R = Ac, R′ = Me).

Reduction of the ketone (II; R = Me, R′ = Ac) to the alcohol (V; R = Me, R′ = H) represents the least satisfactory stage of the process. Stereospecific reduction of the

[1] (*a*) Stodola and Kendall, *J. Org. Chem.*, 1941, **6**, 837; 1942, **7**, 326; (*b*) Butenandt, Schmidt-Thomé, Weiss, Dresler, and Meinerts, *Ber.*, 1939, **72**, 417.
[2] Kuwada, *J. Pharm. Soc. Japan*, 1936, **56**, 75.
[3] Wettstein, Fritzsche, Hunziker, and Miescher, *Helv. Chim. Acta*, 1941, **24**, 332; von Seeman and Grant, *J. Amer Chem. Soc.*, 1950, **72**, 4073.
[4] Sheehan, Coderre, and Cruikshank, *ibid.*, 1953, **75**, 6231.
[5] Meyer and Lindberg, *ibid.*, 1954, **76**, 3033.
[6] Huffman and Lott, *J. Biol. Chem.*, 1948, **172**, 789.
[7] Stodola, Kendall, and McKenzie, *J. Org. Chem.*, 1941, **6**, 841.

ketone (II; R = Ac, R′ = H) to the alcohol (III; R = Ac, R′ = H) with Raney nickel had been reported by Butenandt *et al.*[1b] Stereospecific reduction of the methoxy-ketone (II; R = Me, R′ = Ac) to its alcohol (V; R = Me), in contrast, could not be realised. Huffman and Lott [8] obtained a mixture of alcohols (III; R = Me) and (V; R = Me) by reducing the ketone (II; R = Me) with sodium amalgam, and this probably represents the best route to the required intermediate. Thus we find that Ponndorf reduction of the ketone (II; R = Me, R′ = Ac or H) gives the 16β-isomer almost exclusively, whilst lithium aluminium hydride, sodium borohydride, or sodium in liquid ammonia–ethanol gives the 16β-isomer (III; R = Me) with smaller quantities of the 16α-form (V; R = Me). Epimerisation of the former to the latter through the 16α-toluene-*p*-sulphonate also failed to provide an alternative route, since the ditoluene-*p*-sulphonate was obtained in place of the expected 16-mono-ester.[9] Separation of the 16α-isomer (V; R = Me, R′ = H) from the reduction products of the 16-ketone with sodium amalgam required tedious fractionation, which was more difficult if the ether group was replaced by acetoxyl.[10] Conversion of the ether (V; R = Me, R′ = H)in to the triol (V; R = R′ = H) followed the procedure of Huffman and Lott.[8]



Careful Oppenauer oxidation of the triol (V; R = R′ = H) followed by acetylation furnished the acetoxy-dione (IX; R = Ac) in place of the monoketone (VI; R = Ac). An attempt to prepare the acetate dibenzoate (V; R = Ac, R′ = Bz) for partial hydrolysis at $C_{(3)}$ and then oxidation to the ketone (VI; R = Bz) failed, acetolysis of the ether dibenzoate (V; R = Me, R′ = Bz) with acetic anhydride–toluene *p*-sulphonic acid [6,8] giving a diacetate benzoate. The desired conversion into the dihydroxy-ketone (VI; R = H) was ultimately achieved by microbiological oxidation of the triol (V; R = R′ = H) by *Corynebacterium mediolanum*. Acetylation gave the diacetate (VI; R = Ac), also obtained in very low yield from the ketal (VIII; R = H) by reduction with sodium amalgam, hydrolysis, and acetylation.

Additional transformations carried out included (i) reduction of the ketal-diester

[8] Huffman and Lott, *J. Amer. Chem. Soc.*, (*a*) 1947, **69**, 1835; (*b*) 1949, **71**, 719.
[9] Cf. Elks and Shoppee, *J.*, 1953, 241.
[10] Cf. Huffman, U.S.P. 2,584,271/1952; also refs. 6 and 8.

(VII; R = CO_2Me) with lithium aluminium hydride to the ketal dialcohol (VII; R = CH_2·OH), which was hydrolysed to the keto-dialcohol (IV; R = CH_2·OH), (ii) hydrolysis of 16-hydroxyimino-3β-methoxyandrost-5-en-17-one [6] with sodium sulphite in acetic acid to 3β-methoxyandrost-5-ene-16 : 17-dione, (iii) attempted conversion of 3β-hydroxyandrost-5-en-17-one into androsta-5 : 16-dien-3β-ol by reaction of its toluene-*p*-sulphonylhydrazone with sodium in ethylene glycol,[11] 3β : 17β-diacetoxyandrost-5-ene being isolated after acetylation, (iv) conversion of 3β-acetoxyandrost-5-en-17-one into into 3β : 17-diacetoxyandrosta-5 : 16-diene,[12] followed by treatment of the latter with 1 mol. of perbenzoic acid; alkaline hydrolysis of the total product, followed by acetylation and chromatography, furnished a low yield of 3α : 17β-diacetoxyandrost-5-en-16-one (II; R = R′ = Ac) (cf. Leeds, Fukushima, and Gallagher [13] whose paper appeared subsequently to our experiments).

After completion of the above work, 3β : 16α-diacetoxyandrost-5-en-17-one became available.[14] Its reduction with lithium aluminium hydride proceeded stereospecifically [15] to the triol (V; R = R′ = H), to which this is the most convenient route.

Experimental

Optical rotations refer to $CHCl_3$ solutions in a 1-dm. tube. Ultraviolet absorption spectra in propan-2-ol were kindly determined by Mr. M. T. Davies, B.Sc. Alumina (B.D.H.) of chromatography grade was used.

Methyl 3β-*Hydroxy*-16 : 17-seco*androst*-5-*ene*-16 : 17-*dioate* (I; R = H, R′ = Me) (with Dr. B. Ellis).—(i) Bromine (45 g.) in chloroform (500 ml.) was added during 30 min. to a stirred solution of 3β-acetoxypregna-5 : 16-dien-20-one (100 g.) in chloroform (1 l.) at −60°. The mixture was allowed to warm to room temperature, then the solvent was removed completely under reduced pressure and with the minimum of warming. The viscous residue in acetic acid (2 l.) was treated, with stirring and cooling, with chromium trioxide (85 g.) in 80% acetic acid (600 ml.) dropwise during 1 hr. After 18 hr. at room temperature, zinc dust (300 g.) was added, and the mixture stirred for 45 min., then heated at 100° for 15 min., cooled, and decanted into a large volume of water. The product was isolated with ether, and the ethereal extract washed with water until nearly neutral. Extraction of the ethereal solution with 10% aqueous potassium carbonate, followed by acidification of the alkaline extract, gave the crude ester (I; R = Ac, R′ = H) (36·5—42·5 g.; m. p. 238—245°). Purified from aqueous ethanol, it formed plates, m. p. 262—264°, $[\alpha]_D^{23}$ −97° (*c*, 1·33) (Found: C, 66·7; H, 8·1%; equiv., 190. Calc. for $C_{21}H_{30}O_6$: C, 66·6; H, 8·0%; equiv., 189) (Butenandt *et al.* [15] give m. p. 251°).

(ii) The foregoing ester (I; R = Ac, R′ = H) (30 g.; crude; m. p. 238—245°) in methanol (300 ml.), to which acetyl chloride (5 ml.) had previously been added, was heated under reflux for 1 hr. The mixture was concentrated to half its bulk under reduced pressure, then poured into water, and the product extracted with ether. The dried ethereal extract was treated at 0° with an excess of ethereal diazomethane, the solution acidified with acetic acid and concentrated, and *n*-hexane added to faint turbidity. The dimethyl ester (I; R = H, R′ = Me) (18 g.) separated in needles, m. p. 112° (Kuwada [2] gives m. p. 112°).

In one experiment the product was separated into the 16-methyl ester of 3β-hydroxy-16 : 17-*seco*androst-5-ene-16 : 17-diacid, needles, m. p. 173—177° (from aqueous acetone) (Kuwada [2] gives m. p. 176—177°), and a small proportion of the dimethyl ester, m. p. 112°.

Methyl 3-*Oxo*-16 : 17-seco*androst*-4-*ene*-16 : 17-*dioate* (IV; R = CO_2Me).—A solution of methyl 3β-hydroxy-16 : 17-*seco*androst-5-ene-16 : 17-dioate (10 g.) in *cyclo*hexanone (66 ml.) was added to a solution of aluminium *tert.*-butoxide (10 g.) in toluene (40 ml.), heated under reflux for *ca.* 45 min., then cooled, and water was added. After steam-distillation (*ca.* 10 hr.) the residue was cooled and the solids were collected and used directly for conversion into the 3 : 3-ethylenedioxy-derivative. A portion, on purification from ether–hexane, furnished *methyl* 3-*oxo*-16 : 17-seco*androst*-4-*ene*-16 : 17-*dioate*, m. p. 99—101°, $[\alpha]_D^{24}$ +28° (*c*, 0·524), $\lambda_{max.}$ 239 mμ (log ε 4·24) (Found: C, 68·8; H, 8·2. $C_{21}H_{30}O_5$ requires C, 69·6; H, 8·3%).

Methyl 3 : 3-*Ethylenedioxy*-16 : 17-seco*androst*-5-*ene*-16 : 17-*dioate* (VII; R = CO_2Me).—Crude methyl 3-oxo-16 : 17-*seco*androst-5-ene-16 : 17-dioate (9—10 g., from 10 g. of the

[11] Bamford and Stevens, *J.*, 1952, 4735; cf. Elks, Phillips, Taylor, and Wyman, *J.*, 1954, 1739.
[12] Moffett and Weisblat, *J. Amer. Chem. Soc.*, 1952, **74**, 2183.
[13] Leeds, Fukushima, and Gallagher, *ibid.*, 1954, **76**, 2943.
[14] Cooley, Ellis, Hartley, and Petrow, *J.*, 1955, 4373.

hydroxy-ester) in ethylene glycol (100 ml.) was treated with boron trifluoride–ether complex (10 ml.) for 12 hr. at room temperature. The mixture was decomposed with water, and the precipitated solids were collected, washed with dilute sodium hydrogen carbonate solution and water, and purified from aqueous methanol. *Methyl* 3 : 3-*ethylenedioxy*-16 : 17-*seco*-*androst*-5-*ene*-16 : 17-*dioate* had m. p. 187—189°, $[\alpha]_D^{24}$ −63° (*c*, 0·326) (Found : C, 68·0; H, 8·4. $C_{23}H_{34}O_6$ requires C, 68·0; H, 8·4%).

3 : 3-*Ethylenedioxy*-17β-*hydroxyandrost*-5-*en*-16-*one* (VIII; R = H).—Sodium (800 mg.) was added to a stirred mixture of ether (200 ml.) and liquid ammonia (300 ml.) in a 1-l. three-necked flask fitted with dropping funnel, solid carbon dioxide condenser, and nitrogen inlet. After 30 minutes' stirring methyl 3-ethylenedioxy-16 : 17-*seco*androst-5-ene-16 : 17-dioate (2 g.) was added as a suspension in ether during 1½ hr. The solution was allowed to warm to room temperature, methanol (2 ml.) in ether (100 ml.) added, and the mixture acidified with 5% (w/v) hydrochloric acid (*ca.* 60 ml.). The ethereal layer was removed, washed with water, dried, and evaporated. The aqueous fraction was made alkaline and freed from ether by warming and the separated solids were collected and combined with the solids from the ethereal extract. Crystallisation from ethanol gave 3 : 3-*ethylenedioxy*-17β-*hydroxyandrost*-5-*en*-16-*one*, plates, m. p. 238—241° (sinters at 235°), $[\alpha]_D^{23}$ −125° (*c*, 0·2986) (Found : C, 72·8; H, 8·7. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%).

17β-*Acetoxy*-3 : 3-*ethylenedioxyandrost*-5-*en*-16-*one* (VIII; R = Ac), prepared by acetylation of the foregoing compound (300 mg.) with acetic anhydride–pyridine (10 ml. of each) for 1 hr. on the steam-bath, had m. p. 217—221°, $[\alpha]_D^{24}$ −165° (*c*, 0·504) (Found : C, 70·7; H, 8·3. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·2%).

17β-*Acetoxyandrost*-4-*ene*-3 : 16-*dione* (IX; R = Ac).—(i) 3 : 3-Ethylenedioxy-17β-hydroxyandrost-5-en-16-one (600 mg.; crude) in 90% acetic acid (50 ml.) was heated on the steam-bath for 45 min. The acid was removed under reduced pressure and the residue isolated with chloroform, acetylated, and percolated in benzene through alumina (2 × 0·75 cm.), which was washed with 20 ml. of benzene. The benzene solution was taken to dryness and the residue crystallised from acetone–hexane, to give the diketone (IX; R = Ac), m. p. 196—198°, $[\alpha]_D^{24}$ −48° (*c*, 0·414) (Found : C, 72·9; H, 8·4. Calc. for $C_{21}H_{28}O_4$: C, 73·3; H, 8·1%).

(ii) The ketal (VIII; R = H) (2·4 g.) was heated with methanol (75 ml.) containing water (15 ml.) and concentrated sulphuric acid (3·5 ml.) for 45 min. under reflux. After precipitation with water, isolation with chloroform, and treatment as in (i), the diketone (IX; R = Ac) was obtained, having m. p. 199—200°, not depressed on admixture with the product obtained as in (i) or with a specimen prepared by Stodola and Kendall's [14] method.

Hydrolysis of the foregoing compound (300 mg.) in methanol (30 ml.) with potassium hydrogen carbonate (300 mg.) in water (20 ml.) for 18 hr. at room temperature furnished 16-oxotestosterone, m. p. 160°, $[\alpha]_D^{24}$ −65° (*c*, 0·472) (Found : C, 75·7; H, 8·7. Calc. for $C_{19}H_{26}O_3$: C, 75·5; H, 8·6%) (Meyer and Lindberg [5] give m. p. 152—158°, $[\alpha]_D^{22}$ −52°).

Methyl 3β-*Methoxy*-16 : 17-*seco*-*androst*-5-*ene*-16 : 17-*dioate* (I; R = R′ = Me).—Methyl 3β-hydroxy-16 : 17-*seco*androst-5-ene-16 : 17-dioate (3 g.) was treated with toluene-*p*-sulphonyl chloride (3 g.) in pyridine (20 ml.) overnight at room temperature. The crude toluene-*p*-sulphonate (2 g.) was heated with anhydrous methanol (200 ml.) under reflux for 3 hr.; the mixture was evaporated to small bulk and water added until crystallisation occurred, giving *methyl* 3β-*methoxy*-16 : 17-*seco*-*androst*-5-*ene*-16 : 17-*dioate*, plates, m. p. 87°, $[\alpha]_D^{23}$ −58° (*c*, 0·548) (Found : C, 69·7; H, 8·8. $C_{22}H_{34}O_5$ requires C, 69·8; H, 9·0%), after purification from aqueous methanol.

Treatment of the foregoing compound with sodium–liquid ammonia–ether furnished 17β-hydroxy-3β-methoxyandrost-5-en-16-one, m. p. 188—191°, not depressed on admixture with an authentic specimen.[2b]

3β : 17β-*Dihydroxyandrost*-5-*en*-16-*one* (II; R = R′ = H).—Methyl 3β-acetoxy-16 : 17-*seco*androst-5-ene-16 : 17-dioate (5·46 g.) in ether (540 ml.) was added during 1½ hr. to a solution from sodium (2·4 g.) in liquid ammonia (900 ml.) and ether (600 ml.). Excess of sodium was destroyed with methanol (6 ml.) in ether (300 ml.), and the mixture acidified with 5% (w/v) hydrochloric acid and worked up as before. Crystallisation from aqueous methanol gave 3β : 17β-*dihydroxyandrost*-5-*en*-16-*one*, m. p. 202—205°, $[\alpha]_D^{20}$ −195° (*c*, 0·476) (Found : C, 70·8; H, 8·8. $C_{19}H_{28}O_3.H_2O$ requires C, 70·8; H, 9·3%), probably identical with the product, m. p. 197° (no analysis given), of Butenandt *et al.*[15] (cf. ref. 7).

Acetylation of the foregoing compound gave 3β : 17β-diacetoxyandrost-5-en-16-one,[15] m. p. 123—124°, $[\alpha]_D^{23}$ −183° (*c*, 0·676) (Found : C, 71·0; H, 8·3. Calc. for $C_{25}H_{36}O_5$: C, 71·1; H, 8·2%).

3β-*Methoxy*-16β : 17β-*ditoluene*-p-*sulphonyloxyandrost*-5-*ene* (III; R = Me, R′ = *p*-$C_6H_4Me{\cdot}SO_3$).—The diol (III; R = Me, R′ = H) (200 mg.) in pyridine (2 ml.) was treated at room temperature for 16 hr. with toluene-*p*-sulphonyl chloride (500 mg.), and the product isolated with chloroform. The *diester* formed had m. p. 180—181° (Found: C, 65·2; H, 6·4; S, 11·6. $C_{34}H_{44}O_7S_2$ requires C, 65·0; H, 7·0; S, 10·2%) after crystallisation from acetone–hexane.

Starting material was recovered when the diol (III; R = Me; R′ = H) was treated with 1·1 mol. of toluene-*p*-sulphonyl chloride in pyridine for 5 days at room temperature.

Oxidation of the Triol (V; R = R′ = H) (cf. Ushakov *et al.*[15]).—The triol (500 mg.) in dry benzene (85 ml.) was heated under reflux for 40 min. with aluminium *tert.*-butoxide (1·33 g.) in benzene (12 ml.). Acetone (12 ml.) was added and the mixture heated for a further 18 hr. The product was isolated with ether–chloroform, acetylated, and chromatographed in benzene solution on to alumina (12 g.). The ether to ether–acetone (1 : 1) eluates yielded the diketone (IX; R = Ac), m. p. and mixed m. p. 196° (from acetone–hexane).

16α : 17β-*Dibenzoyloxy*-3β-*methoxyandrost*-5-*ene* (V; R = Me, R′ = Bz), needles, m. p. 200°, $[\alpha]_D^{24}$ −162° (*c*, 0·26) (Found: C, 77·2; H, 7·7. $C_{34}H_{40}O_5$ requires C, 77·3; H, 7·6%), after crystallisation from acetone–hexane, was prepared by treating the ether (V; R = Me, R′ = H) (70 mg.) in pyridine (2 ml.) with benzoyl chloride (1 ml.) for 16 hr. at room temperature.

Treatment of the foregoing compound (230 mg.) in acetic anhydride (9·5 ml.) with toluene-*p*-sulphonic acid (10 mg.) for 1 hr. on the steam-bath gave 3β : 16α(?17β)-*diacetoxy*-17β(?16α)-*benzoyloxyandrost*-5-*ene*, m. p. 148° (from acetone–hexane (Found: C, 72·3; 72·4, H, 6·9, 6·8. $C_{36}H_{38}O_6$ requires C, 72·9; H, 7·7. 3β-Acetoxy-16α : 17β-dibenzoyloxyandrost-5-ene, $C_{38}H_{40}O_6$, requires C, 75·5; H, 7·2%).

16α-*Hydroxytestosterone* (VI; R = H), prepared by microbiological oxidation of (V; R = R′ = H) as described in "Newer Methods of Preparative Organic Chemistry"[16] and crystallised from acetone–hexane, had m. p. 191—192,° $[\alpha]_D^{20}$ +80° (*c*, 0·2596), $\lambda_{max.}$ 240·5 mμ (log ε 4·2) (Found: C, 73·3; H, 9·1. $C_{19}H_{28}O_3.\frac{1}{2}H_2O$ requires C, 72·8; H, 9·3%). The *diacetate* formed needles, m. p. 139—140°, $[\alpha]_D^{23}$ +12° (*c*, 0·259) (Found: C, 71·2; H, 8·4. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%), from acetone–hexane.

Reduction of 3 : 3-*Ethylenedioxy*-17β-*hydroxyandrost*-5-*en*-16-*one* (VIII; R = H).—(i) The ketal (VIII; R = H) (700 mg.) was stirred in ethanol (100 ml.) and acetic acid (9·1 ml.) at 40°, and 5% sodium amalgam (70 g.) added at such rate that the temperature did not exceed 40°. After *ca.* 20 min. 50% acetic acid (7 ml.) was added. When addition of amalgam was complete stirring at room temperature was continued until no more reaction occurred. The product, isolated with ether, was heated with 90% acetic acid (50 ml.) for 45 min. on the steam-bath to remove the ethylenedioxy-residue and after acetylation chromatographed in benzene on alumina (15 g.). Early benzene–ether eluates yielded 16α : 17β-diacetoxyandrost-4-en-3-one, m. p. and mixed m. p. 139—140°.

(ii) The ketal (VIII; R = H) (370 mg.) in ethanol (75 ml.) and acetic acid (4·8 ml.) was stirred at 40° for 2 hr. while 5% sodium amalgam (37 g.) was added. 50% Acetic acid (4 ml.) was added after ½ hr. After 2 hr. a further 10 g. of sodium amalgam were added as rapidly as possible without raising the temperature and stirring continued at 40° for a further hour and at room temperature for an hour. After working up as in (i) and chromatography on alumina, the 20%—50% acetone–ether eluates yielded 16β : 17β-diacetoxyandrost-4-en-3-one, m. p. 198—199° alone or on admixture with an authentic specimen.[15]

3 : 3-*Ethylenedioxy*-16 : 17-seco*androst*-5-*ene*-16 : 17-*diol* (VII; R = $CH_2{\cdot}OH$).—A suspension of the ester (VII; R = CO_2Me) (1·8 g.) in ether (300 ml.) was added dropwise to a boiling suspension of lithium aluminium hydride (2 g.) in ether (200 ml.), after which refluxing was continued for a further hour. The product, isolated in the usual way, crystallised from aqueous methanol, to yield the *diol*, m. p. 182—184°, $[\alpha]_D^{24}$ −47° (*c*, 0·386) (Found: C, 69·9; H, 9·8. $C_{21}H_{34}O_4.\frac{1}{2}H_2O$ requires C, 70·2; H, 9·8%). The *diacetate* had m. p. 105—107°, $[\alpha]_D^{24}$ −30° (*c*, 0·412) (Found: C, 68·6; H, 8·6. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%).

16 : 17-*Dihydroxy*-16 : 17-seco*androst*-4-*en*-3-*one* (IV; R = $CH_2{\cdot}OH$), m. p. 151—152° (from acetone–hexane), $[\alpha]_D^{26}$ +111° (*c*, 0·398) (Found: C, 74·3; H, 9·8. $C_{19}H_{30}O_3$ requires C, 74·5; H, 9·8%), was prepared by hydrolysing the ketal (VII; R = $CH_2{\cdot}OH$) (1 g.) in methanol (30 ml.) and water (6 ml.) with concentrated sulphuric acid (1·5 ml.) for 45 min. under reflux, diluting the mixture with water, and extracting the product with chloroform.

[15] Ushakov and Chinaeva, *J. Gen. Chem.* (*U.S.S.R.*), 1954, **15**, 661.
[16] Fischer, "Newer Methods of Preparative Organic Chemistry," Interscience Publ. Inc., New York, 1948, p. 191.

3β-*Methoxyandrost-5-ene*-16 : 17-*dione*.—Crude 3β-methoxy-16-hydroxyiminoandrost-5-en-17-one [6] (2 g.; m. p. 197—199°) was heated with anhydrous sodium sulphite (20 g.) in acetic acid (80 ml.) for 20 min. on the steam-bath. Water (20 ml.) was then added and heating continued for a further 45 min. The mixture was transferred to a separatory funnel with 3% sodium sulphite solution (800 ml.) and extracted twice with alcohol-free, peroxide-free ether. The ethereal layer was removed and extracted with sodium sulphite solution. The combined sulphite fractions were treated with concentrated hydrochloric acid (*ca.* 200 ml.), and the mixture was heated on the steam-bath for *ca.* 30 min. After being kept at 0° overnight the precipitated solids were collected and purified from acetone–hexane. 3β-*Methoxyandrost-5-ene*-16 : 17-*dione* formed mustard-yellow crystals, m. p. 204—206°, $[\alpha]_D^{28}$ −206° (*c*, 0·294) (Found : C, 75·5; H, 8·9. $C_{20}H_{28}O_3$ requires C, 76·0; H, 8·9%). The compound gave a purple-red colour with concentrated sulphuric acid, but no colour with ferric chloride. Its infrared absorption, kindly determined by Dr. L. J. Bellamy, revealed its existence as >99% as the diketone in the solid state. The *dioxime* had m. p. 230—232° (darkening at 220°) (Found : C, 69·0; H, 9·0; N, 8·5. $C_{20}H_{30}O_3N_2$ requires C, 69·4; H, 8·7; N, 8·1%).

3β-*Hydroxyandrost-5-ene*-17-*one toluene*-p-*sulphonylhydrazone*, m. p. 170—172° (Found : C, 69·5; H, 8·7; N, 5·8; S, 4·5. $C_{34}H_{46}O_3N_2S$ requires C, 68·4; H, 7·9; N, 6·1; S, 7·0%) (1·15 g.), was heated with sodium (5·75 g.) in ethylene glycol (250 ml.) under reflux for 7 hr. Acetylation of the product and purification by chromatography furnished 3β : 17β-diacetoxyandrost-5-ene, m. p. and mixed m. p. 159°.

3β : 17β-*Diacetoxydrost-5-en*-16-*one* (II; R = R′ = Ac).—3β : 17-Diacetoxyandrosta-5 : 16-diene [12] (6·56 g.) was treated with 1 mol. of perbenzoic acid in benzene. After 72 hr. at 0° the product was isolated with ether and hydrolysed by methanol (150 ml.), water (10 ml.), and potassium hydroxide (10 g.) for 1 hr. under reflux, and the material isolated with ether–chloroform. After acetylation at room temperature, the product was chromatographed in benzene on alumina (120 g.). The benzene–ether (1 : 1) to pure ether eluates yielded 3β : 17β-diacetoxyandrost-5-en-16-one, m. p. and mixed m. p. 123°. The ether to ether–acetone (1 : 1) eluates gave a small amount of 3β-acetoxy-5α : 6α-epoxyandrostan-17-one, m. p. and mixed m. p. 215°.

3β : 16α : 17β-*Tripropionyloxyandrost-5-ene* (V; R = R′ = Et·CO).—3β : 16α-Diacetoxyandrost-5-en-17-one [14] (2·72 g.) in ether (250 ml.) was added dropwise during 15 min. to a stirred solution of lithium aluminium hydride (2·1 g.) in ether (250 ml.), and the mixture heated under reflux for 1 hr., after which it was decomposed with ice-water and acidified, the ethereal layer was removed, and the solids were collected and dried. These were extracted (Soxhlet) for 8 hr. with ethyl acetate, and the extract was combined with the ethereal extract and taken to dryness. Part of the residue was acetylated to give 3β : 16α : 17β-triacetoxyandrost-5-ene, m. p. 183—184° (from acetone–hexane) not depressed on admixture with an authentic specimen. The remainder was heated with propionic anhydride–pyridine for 1 hr. on the water-bath, to give 3β : 16α : 17β-*tripropionyloxyandrost-5-ene*, plates, m. p. 149°, $[\alpha]_D^{23}$ −103° (*c*, 0·301) (Found : C, 71·4; H, 9·0. $C_{28}H_{42}O_6$ requires C, 70·9; H, 8·9%).

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62. *Deoxypentose Nucleic Acids. Part IX.* The Electrophoretic Mobility of Sodium Deoxyribonucleate at Various* pH *Values and Ionic Strengths.*

By A. R. Mathieson and J. V. McLaren.

The electrophoretic mobility of sodium deoxyribonucleate has been measured in solutions of ionic strength 0·02—0·2 and pH 3·5—7·0. The net charge on the nucleate ion and its associated gegenions has been calculated from these results and compared with the charge on the nucleate ion itself calculated from electrometric titration data. An estimate has been made of the numbers of sodium and chloride gegenions bound to the nucleate ion at the different pH values and ionic strengths. The titration constants of the bases calculated from the titration curves have been shown to be equal to the dissociation constants of the bases in the nucleic acid molecule.

A number of investigations of the electrophoretic mobility of sodium deoxyribonucleate have been reported.[1] It was thought desirable to repeat this work, some of which was done on more or less degraded material, and to extend it to lower values of pH. The electrophoretic mobility of undegraded sodium deoxyribonucleate of high molecular weight was measured at various pH's and ionic strengths, particularly over the pH range 3—7 where the amino-groups of the purine and pyrimidine bases are being titrated, with consequent rapid alteration in the charge on the nucleate ion. The sample employed, designated G1(II), was sodium deoxyribonucleate of calf thymus extracted by the method of Gulland, Jordan, and Threlfall,[2] being the sample for which the electrometric titration data had been obtained.[3] It was of high molecular weight ($7·9 \times 10^6$ by sedimentation and diffusion [4]) and has been fully described.[3a] This sample is probably better than that used in the earlier study by Creeth, Jordan, and Gulland.[1b]

Results

This sample of sodium deoxyribonucleate migrated as a single boundary under all the conditions of pH and ionic strength studied. Both the boundaries remained sharp during electrophoresis, particularly the ascending boundary. The mobility calculated from the ascending boundary was never more than 2% greater than that calculated from the descending boundary, and so the average of the two values was taken to be the true electrophoretic mobility. No δ or ε boundary was observed, perhaps owing to the relatively low concentration of the nucleate ion and the relatively high concentrations of added salt.

Variation of Mobility with pH *and Ionic Strength.*—The mobilities (μ), determined at different pH's and ionic strengths (I), are plotted in the Figure against I for the various pH values. The ionic strength of the solutions was varied by using sodium chloride as the added electrolyte, and the nucleate concentration was 0·20% in all the experiments. This was not varied, since Creeth, Jordan, and Gulland [1b] showed that the mobility was little affected by the concentration over the range which can be studied in electrophoresis. In view of the effect of concentration on the electrometric titration results, which is only significant [3b] at concentrations below 0·03%, it may be that at these low concentrations the mobility is appreciably influenced by the concentration; clearly the mobility results may not be extrapolated to zero concentration. The extrapolation of the mobilities to zero ionic strength is uncertain at the higher pH values.

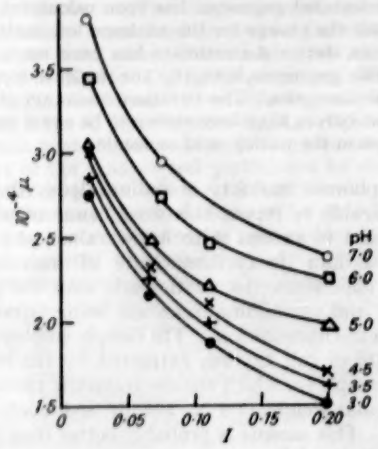
* Part VIII, *J.*, 1956, 158.

[1] (*a*) Stenhagen and Teorell, *Trans. Faraday Soc.*, 1939, **35**, 743; Seibert, *J. Biol Chem.*, 1940, **133**, 593; Hall, *J. Amer. Chem. Soc.*, 1941, **63**, 794; Zittle and Seibert, *J. Immunol.*, 1942, **43**, 47; Cohen, *J. Biol Chem.*, 1942, **146**, 471; (*b*) Creeth, Jordan, and Gulland, *J.*, 1949, 1406 (Part IV), 1409 (Part V).
[2] Gulland, Jordan, and Threlfall, *J.*, 1947, 1129.
[3] Jordan, Mathieson, and Matty, *J.*, 1956, (*a*) 154 (Part VII), (*b*) 158 (Part VIII).
[4] Howard, Thesis, Nottingham, 1953.

Net Charge carried by the Nucleate Ion.—The net charge carried by the nucleate ion and its associated gegenions (Q) can be calculated by Gorin's equation : [5b]

$$\mu = \frac{2Q}{(l + 2a)F'(\kappa a)\pi\eta}\left[\frac{K_0(\kappa a + \kappa r_1)}{(\kappa a + \kappa r_1) \cdot K_1(\kappa a + \kappa r_1)} + \ln\left(\frac{a + r_1}{a}\right)\right]$$

where l and a are respectively the length and radius of the cylindrical colloid particle, r_1 is the average radius of the ions in the ionic atmosphere, κ is the reciprocal Debye–Hückel radius, $F'(\kappa a)$ is a function to account for the random orientation of the particles, η is the coefficient of viscosity of the solvent, and K_0 and K_1 are Bessel functions. Values of $F'(\kappa a)$, K_0, and K_1



The electrophoretic mobility at various pH *values and ionic strengths.*

have been tabulated by Abramson, Moyer, and Gorin.[5b] The length of the nucleate ion is still somewhat uncertain, and the values shown in Table 1 have been employed, based on the results of Rowen [6] and Steiner [7] and the model of a flexible rod. The radius was calculated by using the value 0·50 determined for the partial specific volume, and the molecular weight $7{\cdot}9 \times 10^6$. The value of 2·24 Å was used for r_1 this being the mean of the value for the sodium

TABLE 1. *Dimensions of the nucleate ion.*

I	0·02	0·05	0·10	0·20
Length (l) (Å)	5300	4900	4700	4500
Radius (a) (Å)	19·6	20·6	21·1	21·6

TABLE 2. *The net negative charge carried by the nucleate ion and its associated gegenions.*

	I					
pH	0·02	0·05	0·10	0·15	0·20	0·25 *
3·0	1970	2020	2020	1930	1830	1730
3·5	2040	2100	2030	2000	1990	1940
4·5	2140	2220	2260	2170	2080	2030
5·0	2190	2330	2380	2410	2420	2430
6·0	2460	2620	2700	2730	2760	2780
7·0	2710	2820	2910	2910	2900	2900

* Extrapolated values.

and the chloride ions.[8] κ at 0·5° is $0{\cdot}323 \times 10^8\sqrt{I}$, and η at this temperature is $1{\cdot}76 \times 10^{-2}$ poise. The values of the net charge Q at the various pH and ionic strengths are shown in Table 2.

[5] (*a*) Abramson, Gorin, and Moyer, *Chem Rev.*, 1939, **24**, 345; (*b*) Abramson, Moyer, and Gorin, " Electrophoresis of Proteins," Reinhold Publ. Corpn., New York, 1942.
[6] Rowen, *Biochim. Biophys. Acta*, 1953, **10**, 391.
[7] Steiner, *Trans. Faraday Soc.*, 1952, **48**, 1185.
[8] Gorin, *J. Chem. Phys.*, 1939, **7**, 405.

Discussion

Electrophoretic Mobility and Net Negative Charge.—The Figure shows that μ is decreased by increase in the ionic strength and by lowering the pH of the solution. The decrease in μ at lower pH will be due primarily to the ionisation of the amino-groups, with consequent reduction in the net negative charge on the nucleate ion. The decrease of μ with increase of ionic strength will be due to the increase of interionic attractive forces, and perhaps partly to an increase in the proportion of bound sodium gegenions. At higher ionic strengths the pG' values of the purine and the pyrimidine bases are decreased [3b] and this would lead to an increase of charge with I at the lower pH values. Clearly this effect is masked by the other two. The net negative charge increases sharply with ionic strength up to I ~0·10, thereafter either decreasing (pH 3—4·5) or increasing only very slightly (pH 5—7), and the decrease in the pG' values at higher ionic strengths may be responsible for this. Decrease of pH always leads to a reduction in the net negative charge. The values of the net negative charge depend markedly on the length taken for the nucleate ion.

Comparison of Electrophoretic and Titration Results: Proportion of Bound Gegenions.—The values of the net negative charge (Q_0) on the nucleate ion itself calculated from the results of titration [3b] may be compared with those of the net negative charge (Q) carried by the nucleate ion and its associated gegenions at various pH's and ionic strengths. The difference between these two quantities ($Q_0 - Q$) should be equal to the net positive charge of the bound gegenions, *i.e.*, ($Q_{Na^+} - Q_{Cl^-}$), where Q_{Na^+} and Q_{Cl^-} are the numbers of bound sodium and chloride gegenions, respectively, per nucleate ion.

The value of ($Q_0 - Q$) (Table 3) increases with increase of pH and ionic strength. At pH 6·0 it is a maximum and is virtually constant, decreasing very slightly with increase of I.

Table 3. *The binding of gegenions.*

	$(Q_0 - Q) = Q_{Na^+} - Q_{Cl^-}$						Q_{Cl^-}					
pH \ I	0·02	0·05	0·10	0·15	0·20	0·25	0·02	0·05	0·10	0·15	0·20	0·25
3·5	13,060	14,090	15,080	15,700	16,110	16,660	9940	8910	7920	7300	6890	6340
4·5	19,160	20,080	20,940	21,430	21·910	22,170	3840	2920	2060	1570	1090	830
5·0	21,400	21,930	22,420	22,690	22,990	23,060	1600	1070	580	310	10	0
6·0	23,180	22,990	22,940	22,880	22,860	22,810	0	0	0	0	0	0

Since there are no positively charged sites on the nucleate ion at this pH at the higher ionic strengths, there can be no chloride gegenions directly attached to the nucleate ion. The number of bound sodium gegenions (Q_{Na^+}) when there are no positive sites on the nucleate ion is therefore approximately 23,000, and this is ~90% of the total number of primary phosphoryl groups (25,680). The same proportion has been found from spectroscopic studies.[9] If a significant proportion of chloride ions were bound by the sodium gegenions, Q_{Na^+} would have to be even greater than 23,000 and this seems unlikely. At pH values greater than 3·0 the primary phosphate groups are all ionised, and so the effect of changing the pH from 3·5 to 6·0 on the number of bound sodium ions is not likely to be great. To a first approximation, then, Q_{Na^+} can be taken as 23,000 for all the pH values. The number of chloride ions bound to the charged amino-groups per nucleate ion (Q_{Cl^-}) can therefore be calculated, and these results are also shown in Table 3. The values of Q_{Cl^-} are quite reasonable, increasing rapidly as the pH is lowered and the number of charged amino-groups increased. The proportion of the amino-groups which are ionised at a given pH and ionic strength may be calculated from the pG' values of the bases given in Table 1 of the preceding paper, and comparison with the values of Q_{Cl^-} in Table 3 then shows that the fraction of charged amino-groups which have a bound chloride ion increases rapidly as the pH is lowered, becoming just less than unity at pH 3·5. This is similar to the behaviour of polyacrylic acid with sodium gegenions when the degree of ionisation of the acid is increased.[10]

[9] Lawley, personal communication.
[10] Huizenga, Greiger, and Wall, *J. Amer. Chem. Soc.*, 1950, **72**, 2636.

The net charge on the nucleate ion is always negative. The possibility exists therefore that this might preclude the binding of chloride ions owing to electrostatic repulsion. However, the binding of chloride ions to the deoxyribonucleate ion has been observed by Shack, Jenkins, and Thompsett [11] who concluded, from membrane potential measurements and chemical analysis after dialysis equilibrium, that 0·32 ion of chloride was bound per four atoms of phosphorus. Moreover, if no chloride ion is bound it must be assumed that a decrease of bound sodium ion occurs on increase of sodium-ion concentration, to explain their results. No evidence of this was found.

It is also known that chloride ions are bound by certain proteins. Thus Alberty and Marvin's results [12] show that the chloride ions are bound to bovine serum albumin between pH's of 7·0 and 3·2, although the isoelectric point of this protein is 4·9.

Comparison of Electrophoretic and Titration Results: Dissociation Constants.—Katchalshy, Shavit, and Eisenberg [13] have shown that the titration of a weak polymeric electrolyte can be represented by the expression

$$\mathrm{pH} = \mathrm{p}K_0 - \log\frac{\beta}{1-\beta} - \frac{0{\cdot}4343e\psi}{kT}$$

where β is the degree of dissociation and ψ is the electrostatic potential. Only if the term involving ψ is negligible can the titration constants of the bases (pG'), given by $\mathrm{pH} = \mathrm{p}G' - \log[\beta/(1-\beta)]$, be identified with the dissociation constants (pK_0) of the bases in the nucleate. This term is not negligible for simple polyelectrolytes.

The value of ψ can be calculated from the electrophoretic data. ψ is related to the electrophoretic mobility by the equation $\psi = 300\,\eta\mu/CD$, where D is the dielectric constant of the medium, and C is a factor which depends on the shape and orientation of the migrating ion. If the nucleate ion can be treated as a long cylinder orientated randomly with respect to the field, $C = 1/\pi F'(\kappa a)$ (Abramson, Moyer, and Gorin [56]). Table 4 shows the values of ψ and of $0{\cdot}4343e\psi/kT$ for various pH values at $I = 0{\cdot}10$.

TABLE 4. *The electrostatic potential* ($I = 0{\cdot}10$).

pH	3·0	3·5	4·5	5·0	6·0	7·0
$10^4\psi$	2·23	2·35	2·47	2·56	2·90	3·20
$0{\cdot}4343e\psi/kT$	1·14	1·20	1·26	1·30	1·48	1·63

The term $0{\cdot}4343e\psi/kT$ varies only slightly with pH (only 0·1 pH unit for a change of pH of unity) and so causes no appreciable spread of the titration curves. This observation, which explains the success of Gulland, Jordan, and Taylor [14] in identifying the titration constants of nucleic acid with the bases concerned, is different from the behaviour of synthetic polyelectrolytes. It may be that the presence of the large gegenion atmosphere and the overlapping nature of the dissociations concerned are responsible for this. The magnitude of $0{\cdot}4343e\psi/kT$ accounts correctly for the departure of the value of pG' from pK_0 at finite concentrations and ionic strengths.

EXPERIMENTAL

Preparation and Analysis of the Solutions.—Undried sodium deoxyribonucleate was dissolved in water without stirring to give a stock solution of twice the desired concentration, which was kept at 0°. Samples of this solution were diluted with equal volumes of buffer solutions of twice the desired ionic strength. These solutions were then dialysed against the appropriate buffer solution for 17 hr. The buffer solutions contained sodium chloride to give the desired ionic strength, and virtually all the ionic strength of the buffer solutions was due to this. The buffer solutions [15] were: glycine–hydrochloric acid for pH 3·5, acetate for pH 4·5 and 5·0, and phosphate for pH 6·0 and 7·0.

[11] Shack, Jenkins, and Thompsett, *J. Biol. Chem.*, 1952, **198**, 85.
[12] Alberty and Marvin, *J. Amer. Chem. Soc.*, 1951, **73**, 3220.
[13] Katchalsky, Shavit, and Eisenberg, *J. Polymer Sci.*, 1954, **13**, 69.
[14] Gulland, Jordan, and Taylor, *J.*, 1947, 1131.
[15] Cf. Miller, *Arch. Biochem.*, 1950, **29**, 420.

The nucleate concentration of the stock solution was determined by the method of Jones, Lee, and Peacocke.[16]

Electrophoretic Mobility.—The mobilities were determined at 0·5° in a modified form of the Tiselius electrophoresis apparatus [17] constructed by Adam Hilger, Ltd. The methods used were those described by Creeth, Jordan, and Gulland.[15] The conductivities were determined by the use of a Mullard conductance bridge, and the pH of the solutions was measured electrometrically to ±0·01 pH unit with a Tinsley potentiometer, a standard Weston cell, a hydrogen electrode, and a standard silver–silver chloride electrode.

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Department of Chemistry, The University, Nottingham. [*Received, July 15th*, 1955.]

[16] Jones, Lee, and Peacocke, *J.*, 1951, 623.
[17] Tiselius, *Trans. Faraday Soc.*, 1937, **33**, 524.

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63. *The Reaction of Cyanamide with α-Amino-acetals and α-Amino-aldehydes.*

By Alexander Lawson.

2-Aminoglyoxalines (II) are obtained in good yield by the action of cyanamide on α-amino-acetals followed by hydrolysis and ring closure. A number of α-amino-esters have been reduced by the Akabori method and condensed with cyanamide to give, after ring closure, the glyoxalino-glyoxalines (IV).

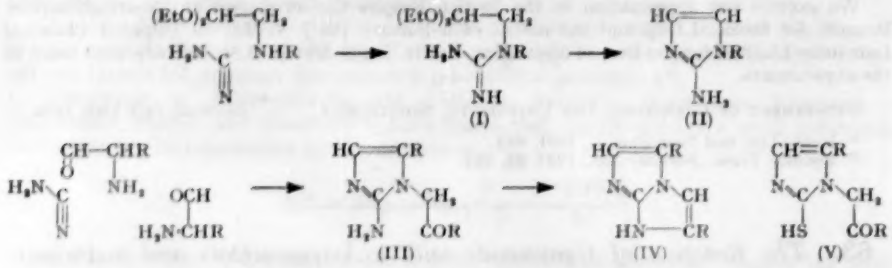
The preparation of 2-aminoglyoxaline and its derivatives has been described by Pyman and his co-workers [1] and by De Cat and van Dormael.[2] They introduced the amino-group into a preformed glyoxaline ring by the reduction of a *para*-substituted 2-phenylazoglyoxaline obtained by condensing the diazonium compound with the glyoxaline. Theoretically, an obvious route to 2-aminoglyoxalines is the condensation of cyanamide with α-aminocarbonyl compounds, but Norris and McKee [3] reported that condensations of *p*-chlorophenacylamine hydrochloride with cyanamide, dicyandiamide, and sodium dicyandiamide were unsatisfactory though they obtained moderate yields of 2-guanidinoglyoxalines from *p*-chlorophenacylamine hydrochloride and various cyanoguanidines. Leonard, Curtin, and Beck [4] describe the preparation of 2-aminobenziminazole derivatives by condensing *o*-phenylenediamines with cyanogen bromide, a method originally used by Ziegelbauer.[5]

No crystalline material could be isolated on reaction of aminoacetaldehyde with cyanamide at various pH, presumably because the conditions favourable for the condensation led to decomposition of the amino-aldehyde. However the amino-acetal reacted smoothly in acetic acid, giving the acetate of the diethoxyethylguanidine (I; R = H) which on treatment with hydrochloric acid cyclised to the hydrochloride of the strongly basic 2-aminoglyoxaline [16] (II; R = H). In addition to the derivatives described by Pyman *et al.* 2-acetamidoglyoxaline hydrochloride was prepared, which crystallised as the monohydrate and gave 2-acetamidoglyoxaline, prepared by Pyman *et al.*, on treatment with sodium carbonate. Although 2-aminoglyoxaline is only a monoacidic base, like guanidine itself, the acetyl derivative still apparently retains considerable basicity.

In a similar way *N*-methylamino-acetal on reaction with cyanamide followed by ring closure gave 2-amino-1-methylglyoxaline (II; R = Me).

[1] Pyman and co-workers, *J.*, (*a*) 1919, **217**; (*b*) 1920, 1426; (*c*) 1925, 2012.
[2] De Cat and van Dormael, *Bull. Soc. chim. belges*, 1950, **59**, 273.
[3] Norris and McKee, *J. Amer. Chem. Soc.*, 1955, **77**, 1056.
[4] Leonard, Curtin, and Beck, *ibid.*, 1947, **69**, 2459.
[5] Ziegelbauer, *Monatsh.*, 1896, **17**, 653.

In order to account for the formation of glyoxalinothiazoles by reaction between thiocyanate and amino-aldehydes at pH 4, it was postulated [6] that the latter substances underwent a Schiff's base condensation with subsequent deamination. Something about the behaviour of amino-aldehydes under conditions at which condensation with cyanamide might be expected to take place being therefore known, it seemed worth while to attempt such condensations using the solution resulting from the Akabori reduction [7] of amino-esters. In the case of alanine ester, reaction between the α-aminopropionaldehyde in solution at pH 4 and cyanamide gave the glyoxalinoglyoxaline (IV; R = Me) in about 30% yield.



With the esters of leucine, norleucine, α-amino-octanoic acid, and phenylalanine, boiling the solutions containing the amino-aldehydes with cyanamide gave varying yields of sparingly soluble hydrochlorides of bases which on the evidence of the analytical results, the absence of typical aldehyde properties, and their ability to give oximes, have been assigned the structure of 5-alkyl-2-amino-1-oxoalkylglyoxalines (III) [analogous glyoxalinyl ketones (V) were obtained from the corresponding reaction between the amino-aldehydes and thiocyanate [6]]. The hydrochlorides of these bases (III) on treatment with acetic anhydride gave acetyl derivatives similar to those described for the simpler 2-aminoglyoxalines above. From the compounds (III) the glyoxalinoglyoxalines (IV) were obtained either by the action of hydrochloric acid or, as in the case of the phenylalanine derivative, by spontaneous ring closure of the corresponding free base.

The filtrates from the hydrochlorides of the bases (III), when made alkaline and extracted with ether, gave, together with some unchanged amino-ester, considerable quantities of non-crystalline basic material. This, together with the products obtained similarly from other amino-esters which did not give sparingly soluble hydrochlorides, are being further examined. Guanidine derivatives appear to be present since crystalline picrates obtained gave the Jaffé reaction.

Experimental

N-(2 : 2-Diethoxyethyl)guanidine (I; R = H).—Aminoacetaldehyde diethyl acetal (4 g.) was heated for 1 hr. on a water-bath with cyanamide (2·5 g.) dissolved in water containing a few drops of acetic acid.[8] After concentration under reduced pressure, the residual syrup was triturated with anhydrous ether, and the gummy residue treated with acetone (30 ml.) to give the colourless crystalline *guanidine acetate* (1·8 g.). Recrystallisation from ethanol–ether gave prisms, m. p. 139—140° (Found: C, 45·8; H, 8·7; N, 17·7. $C_7H_{17}O_2N_3,CH_3{\cdot}CO_2H$ requires C, 45·9; H, 8·9; N, 17·8%).

2-Aminoglyoxaline (II; R = H).—The above acetate (1 g.) was warmed in concentrated hydrochloric acid (3 ml.) for a few min. on the water-bath. Water was added and evaporation of the solution to dryness under reduced pressure, and again after addition of water, left the crystalline 2-aminoglyoxaline hydrochloride (quantitative yield) which on recrystallisation from ethanol–ether (somewhat hygroscopic plates) had m. p. 155° (Fargher and Pyman [14] found 152°) (Found: C, 29·7; H, 5·1; N, 34·9. Calc. for $C_3H_5N_3,HCl$: C, 30·1; H, 5·1; N, 35·1%). This gave a picrate, felted needles (from ethanol), m. p. 231°, and the acetyl derivative had m. p. 285° (decomp.). *2-Acetamidoglyoxaline hydrochloride*, prepared by warming the hydrochloride

[6] Lawson and Morley, *J.*, 1955, 1695.
[7] Akabori, *Ber.*, 1933, **67**, 151.
[8] Kurzer and Lawson, *Org. Synth.*, 1954, **34**, 67.

with acetic anhydride for a few min. and recrystallising the product from ethanol, gave needles, m. p. 143° (Found : C, 33·5; H, 5·5; N, 23·4. $C_5H_7ON_3,HCl,H_2O$ requires C, 33·4; H, 5·6; N, 23·4%).

N-2 : 2-*Diethoxyethyl*-N-*methylguanidine* (I; R = Me).—The *acetate* (5·0 g.) obtained as above from methylaminoacetaldehyde diethyl acetal (5·5 g.) and a solution of cyanamide (5 g.) in aqueous acetic acid, and recrystallised from alcohol–ethyl acetate, had m. p. 202° (needles) (Found : C, 48·2; H, 9·3; N, 16·6. $C_8H_{19}O_2N_3,CH_3{\cdot}CO_2H$ requires C, 48·2; H, 9·2; N, 16·8%). The *picrate* (needles from water) had m. p. 117° (Found : C, 40·3; H, 5·5; N, 20·0. $C_{14}H_{22}O_9N_6$ requires C, 40·3; H, 5·3; N, 20·1%).

2-*Amino*-1-*methylglyoxaline* (II; R = Me).—The *hydrochloride*, obtained from the acetal by the above method in quantitative yield, had m. p. 84° (prismatic needles from ethanol–ethyl acetate) (Found : C, 31·5; H, 6·7; N, 27·6. $C_4H_7N_3,HCl,H_2O$ requires C, 31·7; H, 6·6; N, 27·7%). The *picrate* (prisms from aqueous ethanol) had m. p. 212° (Found : C, 36·9; H, 3·1. $C_{10}H_{10}O_7N_6$ requires C, 36·8; H, 3·1%). The free base obtained by extraction of an alkaline solution of the hydrochloride with chloroform and purified by distillation at 12 mm. was too hygroscopic for analysis. It was sparingly soluble in ether and benzene. The hydrochloride, warmed with acetic anhydride, give an *acetyl derivative* (needles from aqueous ethanol), m. p. 141° (Found : C, 37·1; H, 6·1; N, 21·6. $C_6H_9ON_3,HCl,H_2O$ requires C, 37·1; H, 6·2; N, 21·7%).

2 : 3-*Dihydro*-4 : 5′-*dimethylglyoxalino*(1′ : 2′-1 : 2)*glyoxaline* (IV; R = Me).—DL-α-Alanine (10 g.) was esterified with ethanol and reduced with sodium amalgam as previously described.[6] To the solution of the resulting amino-aldehyde, cyanamide (10 g.) in 10% aqueous acetic acid (60 ml.) was added and the mixture brought to pH 4·0—5·0 and boiled for 30 min. The cooled and filtered solution was then made alkaline with solid sodium hydrogen carbonate and extracted with ether to remove unused cyanamide and dicyandiamide. Sodium hydroxide was next added and the solution again extracted with ether. The ether solution after drying (Na_2SO_4) was evaporated and anhydrous hydrogen chloride passed into the residue dissolved in a little anhydrous ether. The dark precipitated *hydrochloride* (3·2 g.) recrystallised from ethanol as colourless prisms, m. p. 272° (decomp.) (Found : C, 49·1; H, 6·1; N, 24·3. $C_7H_9N_3,HCl$ requires C, 49·0; H, 5·8; N, 24·5%). The free *base*, prisms (from ethanol), m. p. 125°, was extracted from an alkaline solution of the hydrochloride with chloroform (Found : C, 61·8; H, 6·7; N, 31·0. $C_7H_9N_3$ requires C, 62·1; H, 6·7; N, 31·1%). The *picrate*, needles (from ethanol), had m. p. 226° (Found : C, 43·0; H, 3·4; N, 23·0. $C_{13}H_{12}O_7N_6$ requires C, 42·8; H, 3·3; N, 23·0%).

2-*Amino*-5-isobutyl-1-(4-*methyl*-2-*oxopentyl*)*glyoxaline* (III; R = Bu^i).—L-Leucine (10 g.), esterified and reduced as above, was condensed with cyanamide at pH 5·0. The resulting solution was filtered and cooled to give a precipitate of the *hydrochloride* (3 g.) which crystallised from water as flat needles, m. p. 179° (Found : C, 55·4; H, 8·8; N, 14·5. $C_{13}H_{23}ON_3,HCl$ requires C, 56·8; H, 8·8; N, 15·3%). The free *base*, needles from benzene–light petroleum, had m. p. 118° (Found : C, 66·0; H, 9·7; N, 17·6. $C_{13}H_{23}ON_3$ requires C, 65·9; H, 9·7; N, 17·7%). The *picrate*, felted needles from ethanol, had m. p. 214° (Found : C, 49·1; H, 5·6. $C_{19}H_{25}O_8N_6$ requires C, 49·2; H, 5·6%). By the action of acetic anhydride at 100° on the above hydrochloride there was obtained an *acetyl derivative*, needles (from aqueous ethanol), m. p. 151° (Found : C, 54·1; H, 8·2. $C_{15}H_{25}O_2N_3,HCl,H_2O$ requires C, 54·0; H, 8·4%).

4 : 5′-*Diisobutyl*-2 : 3-*dihydroglyoxalino* (1′ : 2′-1 : 2)*glyoxaline* (IV; R = Bu^i).—The above hydrochloride (0·5 g.) was warmed on the boiling-water bath with concentrated hydrochloric acid (10 ml.) for 4 hr. Water was added and after removal of a little unchanged starting material by filtration the solution was evaporated under reduced pressure and again after the addition of ethanol. The oily residue (0·3 g.) was crystallised from ethyl acetate–ethanol to give the somewhat hygroscopic *hydrochloride* as flat prisms, m. p. 113° (Found : C, 59·5; H, 8·7; N, 15·9. $C_{13}H_{21}N_3,HCl$ requires C, 61·0; H, 8·6; N, 16·4%). The *picrate*, prepared from the hydrochloride, recrystallised from ethanol as needles, m. p. 128° (Found : C, 50·9; H, 5·5. $C_{19}H_{24}O_7N_6$ requires C, 50·9; H, 5·4%).

2-*Amino*-5-n-*butyl*-1-2′-*oxohexylglyoxaline* (III; R = Bu^n).—DL-Norleucine (10 g.), esterified, reduced, and condensed with cyanamide as in the case of leucine (above), gave the *hydrochloride* (2·7 g.) as plates, m. p. 160° (from aqueous ethanol) (Found : C, 55·8; H, 8·8; N, 15·5. $C_{13}H_{23}ON_3,HCl$ requires C, 56·9; H, 8·8; N, 15·3%). The free *base*, felted needles from benzene–light petroleum, had m. p. 94° (Found : C, 65·4; H, 9·7; N, 17·8. $C_{13}H_{23}ON_3$ requires C, 65·7; H, 9·7; N, 17·7%). The *picrate*, felted needles from ethanol, had m. p. 190° (Found : C, 49·0; H, 5·4. $C_{19}H_{25}O_8N_6$ requires C, 49·1; H, 5·6%). The *oxalate*, needles from water, had m. p. 177° (Found : C, 54·6; H, 7·2; N, 12·3. $C_{13}H_{23}ON_3,H_2C_2O_4$ requires C, 55·0;

H, 7·6; N, 12·8%). An *acetyl derivative* prepared as in the case of the leucine isomer (above) crystallised from ethanol as felted needles, m. p. 149° (Found : C, 54·6; H, 8·3. $C_{15}H_{25}O_3N_3$,HCl,H_2O requires C, 54·0; H, 8·4%). The *oxime hydrochloride*, plates from water, had m. p. 150° (Found : C, 54·2; H, 8·8. $C_{13}H_{24}ON_4$,HCl requires C, 54·1; H, 8·7%).

4 : 5′-*Dibutyl*-2 : 3-*dihydroglyoxalino*(1′ : 2′-1 : 2)*glyoxaline* (IV; R = Bu^n).—Ring closure of the above hydrochloride as in the previous case gave the hygroscopic *hydrochloride*, prisms (from ethyl acetate–ethanol), m. p. 111° (Found : C, 61·2; H, 8·6; N, 15·8. $C_{13}H_{21}N_3$,HCl requires C, 61·0; H, 8·6; N, 16·4%). The *picrate*, needles from ethanol, had m. p. 131° (Found : C, 51·0; H, 5·3. $C_{19}H_{24}O_7N_6$ requires C, 50·9; H, 5·4%).

2-*Amino*-5-*hexyl*-1-2′-*oxo*-*octylglyoxaline* (III; R = C_6H_{11}).—The *hydrochloride* was prepared as above from DL-α-amino-octanoic acid and recrystallised from ethanol as felted needles, m. p. 167° (yield 10%) (Found : C, 61·0; H, 9·8; N, 12·5. $C_{17}H_{31}ON_3$,HCl requires C, 61·8; H, 9·7; N, 12·7%). The free *base*, felted needles from benzene–light petroleum, had m. p. 98° (Found : C, 68·9; H, 10·6; N, 14·3. $C_{17}H_{31}ON_3$ requires C, 69·6; H, 10·6; N, 14·3%). The *picrate*, needles from ethanol, had m. p. 185° (Found : C, 52·5; H, 6·6. $C_{23}H_{34}O_8N_6$ requires C, 52·8; H, 6·5%).

2-*Amino*-5-*benzyl*-1-(2-*oxo*-3-*phenylpropyl*)*glyoxaline* (III; R = CH_2Ph).—The *hydrochloride* prepared as above from phenylalanine crystallised from aqueous ethanol as felted needles, m. p. 193° (decomp.) (yield 32%) (Found : C, 66·8; H, 5·9; N, 11·8. $C_{19}H_{19}ON_3$,HCl requires C, 66·9; H, 5·9; N, 12·3%). The *picrate*, prepared from the hydrochloride and recrystallised from ethanol, had m. p. 219° (Found : C, 56·1; H, 4·3. $C_{25}H_{23}O_8N_6$ requires C, 56·1; H, 4·1%). The *oxime hydrochloride*, needles from water, had m. p. 171° (Found : C, 60·9; H, 6·0; N, 15·1. $C_{19}H_{20}ON_4$,HCl,H_2O requires C, 60·9; H, 6·1; N, 14·9%).

4 : 5′-*Dibenzyl*-2 : 3-*dihydroglyoxalino*(1′ : 2′-1 : 2)*glyoxaline* (IV; R = CH_2Ph).—The *base* was obtained from the above hydrochloride by addition of alkali to an aqueous solution and extraction with ether. It crystallised from aqueous ethanol in prismatic needles, m. p. 164° (Found : C, 79·4; H, 6·1; N, 15·1. $C_{19}H_{17}N_3$ requires C, 79·5; H, 5·9; N, 14·6%). The *picrate*, needles from ethanol, had m. p. 182° (Found : C, 57·9; H, 3·7. $C_{25}H_{20}O_7N_6$ requires C, 58·1; H, 3·9%).

I thank Mr. J. O. Stevens for technical assistance, and British Schering Research Institute for a gift of methylamino-acetal.

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64. *Enol Isomerism in the Tropine Series.*

By C. A. FRIEDMANN and J. M. Z. GLADYCH.

Two α-hydroxymethyleneacetyltropeines have been isolated and shown to be geometrical isomers about the enolic double bond.

DURING an unsuccessful attempt to prepare atropine by the hydrogenation of α-formylphenylacetyltropeine (I*a*), we had recourse to Asahina and Nogami's method (*Proc. Imp. Acad., Tokyo*, **1946**, **16**, 229) for the preparation of the latter, which had been isolated in yields of about 40% by the action of ethyl formate on phenylacetyltropeine in the presence of sodium methoxide. However, in addition to a relatively insoluble solid product (I*a*), we isolated, in comparable yield, a yellow-brown oil (I*b*) which was apparently overlooked by the Japanese authors. Both products are soluble in dilute aqueous sodium hydroxide but insoluble in aqueous sodium hydrogen carbonate, and give an intense violet colour with ferric chloride solution. Both reduce ammoniacal silver nitrate, but only the oil reduces Fehling's solution and gives a copper salt. Hydrolysis with aqueous-alcoholic sodium hydroxide converts both substances quantitatively into tropine and phenylacetic acid, the oil faster than the solid. The compounds give different, crystalline enol benzoates (II), $C_{24}H_{25}O_4N$.

The chemical behaviour of the compounds (I*a* and *b*) was consistent with their being isomeric α-hydroxymethylenephenylacetyltropeines, and the elaboration of their relationship rested mainly on spectral evidence.

The solid existed entirely in the enolic form (absence of ketonic band in the 1730 cm.$^{-1}$ region; see Table), whereas the oil was probably a tautomeric mixture of enol and aldehyde (bands at 1735, 1700, and 1653 cm.$^{-1}$). As the salt-like properties of the solid seemed to point to strong bonding interaction between the enolic hydroxyl and the tertiary amine group, it was important to ascertain whether this interaction arose from internal or external bonding. Since the compound was virtually insoluble in both carbon tetrachloride and carbon disulphide, infrared spectra were of little value in the 3000 cm.$^{-1}$ region, characteristic of the OH stretching vibrations.

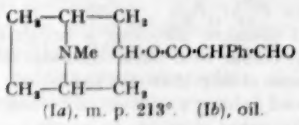
Examination of Catalin models of the compounds (I*a*), and approximate calculations using standard bond lengths, have shown that chelation, such as that represented in (III), could occur only (*a*) if the tropan ring were forced into the boat rather than the normally accepted chair configuration, and (*b*) if the enolic hydroxyl group were in the *cis*-relation [about the αβ-double bond; (III)] to the tropan skeleton. This structure would require rotation of $C_{(3)}$ to the same side of the plane as >NMe, and change the conformation of the ester group attached to this carbon atom from axial to equatorial.

Although a comparison of the carbon–oxygen stretching bonds of the compound (I*a*) in the 1100—1200 cm.$^{-1}$ region with those of the benzoates shows a definite hypsochromic shift, comparable to that observed in passing from axial to equatorial conformations in steroids (Page, *J.*, 1955, 2017), assignment of configuration on these grounds is open to doubt since the spectrum of the solid was measured in Nujol mull and because of possible interaction with the enolic hydroxyl group.

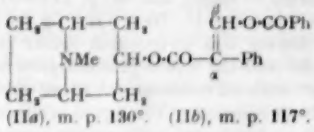
Main infrared absorption peaks (cm.$^{-1}$) (in CCl_4 solution, except where stated).

Substance	Carbonyl	Enol	Ester (C–O)	Substance	Carbonyl	Enol	Ester (C–O)
(I*a*) (Nujol) ...	1648	—	1150, 1255	(II*a*)	1730, 1700	—	1116, 1240
(I*b*)	1735, 1700	1653	—	(II*b*)	1730, 1710	—	1120, 1240

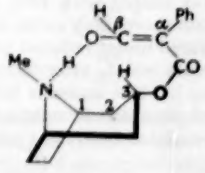
The spectra of the enol benzoates, however, gave considerable information. The marked similarity of the curves throughout the range 1650—700 cm.$^{-1}$ is consistent with their being geometrical isomers about the enolic double bond. Similar isomerism of enol benzoates has been observed in the case of 2 : 2-diphenylethyl 2 : 4 : 6-trimethylphenyl ketone by Nesmeyanov, Sazanowa, and Vasileva (*Izvest. Akad. Nauk S.S.S.R., Otdel Khim. Nauk*,



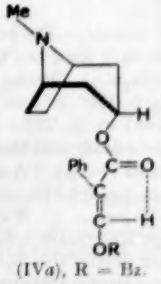
(I*a*), m. p. 213°. (I*b*), oil.



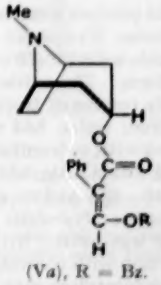
(II*a*), m. p. 130°. (II*b*), m. p. 117°.



(III)



(IV*a*), R = Bz.
(IV*b*), R = H.



(V*a*), R = Bz.
(V*b*), R = H.

1952, 78). The absorption peaks of the two ester-carbonyl groups appear at 1700 and 1730 cm.$^{-1}$ in the benzoate (II*a*) and at 1710 and 1730 cm.$^{-1}$ in the isomer (II*b*), that at 1700 and 1710 cm.$^{-1}$ being due to the ester attached to $C_{(3)}$ of the tropane skeleton and that at 1730 to the enol benzoate. The slight bathochromic shift (10 cm.$^{-1}$) of the C=O stretching band (cf. IV*a*) suggests greater hydrogen bonding in this than in the isomer (V*a*), which is

possible only if the enol-ester group is *trans* about the double bond to the tropan ring [cf. (IV*a*)]. Since this enol benzoate (IV*a*) arose from the solid enol (I*a*) by treatment with benzoyl chloride and sodium hydroxide, the latter must have the spatial arrangement indicated in (IV*b*) which cannot be internally chelated, since the enolic hydroxyl is not within bonding distance of the >NMe group. The compound (I*a*) is thus intermolecularly hydrogen bonded, a finding confirmed by its high melting point and salt-like behaviour, by its comparative insolubility in organic solvents, and by its failure to give a copper enolate (Henecka, *Chem. Ber.*, 1948, **81**, 189). The enol benzoate, m. p. 117°, therefore has the spatial structure (V*a*), and its enolic progenitor contained in the oil (I*b*) can be represented by (V*b*).

Assignment of the same configuration (probably chair) for the tropan ring in both enol benzoates rests on the similarity of the C–O stretching frequencies attributable to the ester group at $C_{(3)}$, in the 1100—1200 cm.$^{-1}$ region.

Experimental

α-Formylphenylacetyltropeine (I*a and b*).—Freshly cut sodium (2·9 g.) was emulsified at 140° in anhydrous xylene (100 c.c.), containing one drop of oleic acid. Then anhydrous ethanol (5·8 g.) was added. When most of the sodium had dissolved, a mixture of phenylacetyltropeine (32 g.; Hromatka, Csoklich, and Hofbauer, *Monatsh.*, 1952, **83**, 1321) and ethyl formate (11·9 g.) was added dropwise at 15—20°. The mixture was stirred for 3 hr. and poured into 1% sodium hydroxide solution (100 c.c.) with stirring and ice-cooling. The alkaline layer was washed with a little benzene, and the pH adjusted to 7·5 with 10% hydrochloric acid. The precipitated semi-solid product was extracted with chloroform, and the extract washed with saturated sodium chloride solution until neutral. After a few minutes, the crystalline material (5·0 g.) which had been deposited was collected, washed with a little alcohol and ether, and dried *in vacuo*. It had m. p. 212—213° (decomp.).

The filtrate was dried (Na_2SO_4) and concentrated *in vacuo* to the point of crystallization, yielding a second crop of solid (2·0 g.). For analysis, a sample was dissolved in dilute hydrochloric acid at 20°, the solution treated with charcoal and filtered, and dilute aqueous ammonia was added to pH 7·5. The colourless crystals, washed successively with water, alcohol, and ether, and dried *in vacuo*, had m. p. 212—213° (decomp.) (Asahina and Nogami, *loc. cit.*, give m. p. 214°) (Found: C, 70·6; H, 7·6. Calc. for $C_{17}H_{21}O_3N$: C, 70·9; H, 7·3%). The chloroform filtrate was evaporated under reduced pressure, affording a brown oil (10·4 g.). Both the solid and the liquid product gave a violet colour with ferric chloride solution. The solid product reduced ammoniacal silver nitrate more slowly than did the liquid, and did not reduce Fehling's solution. The liquid product reduced Fehling's solution on boiling and afforded a copper salt on treatment with copper acetate. Repeated attempts to isolate a copper salt of the solid product were unsuccessful.

Alkaline Hydrolysis of the Liquid Isomer.—The oil (2·0 g.) was heated with 20% sodium hydroxide solution (20 c.c.) on a steam-bath for 2 hr., then cooled and thoroughly extracted with chloroform. The extract was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The oily residue of tropine (1·0 g.; b. p. 120°/20 mm.) gave a picrate which, after recrystallization from water, had m. p. and mixed m. p. 285—286° (decomp.). The aqueous layer was acidified with concentrated hydrochloric acid, and the precipitated phenylacetic acid collected, washed with a little cold water, and dried (0·8 g.). A sample recrystallized from light petroleum (b. p. 40—60°) had m. p. and mixed m. p. 75—76°.

Alkaline Hydrolysis of the Solid Isomer.—(i) *With aqueous sodium hydroxide.* The solid (2·0 g.) was heated with 40% sodium hydroxide solution (20 c.c.) on a steam-bath for 2 hr. Extraction with chloroform gave, after drying (Na_2SO_4) and removal of solvent, an oily residue of phenylacetyltropeine (1·2 g.). The picrate, after recrystallization from water, had m. p. and mixed m. p. 169—170° (Asahina and Nogami, *loc. cit.*, give m. p. 169°). No phenylacetic acid was isolated from the aqueous layer.

(ii) *With ethanolic potassium hydroxide.* The solid (1·0 g.) was heated with ethanolic potassium hydroxide (50%; 10 c.c.) on a steam-bath for 3 hr. The solution was cooled, diluted with water, and thoroughly extracted with chloroform. The extract, after removal of solvent, afforded a residue of tropine (0·5 g.) which crystallized. It gave a picrate, m. p. and mixed m. p. 286—287° (decomp.). Acidification of the alkaline layer with concentrated hydrochloric

acid afforded phenylacetic acid (0·5 g.), which was washed with a little water and dried. A sample recrystallized from light petroleum had m. p. and mixed m. p. 75—76°.

Enol Benzoates.—(*a*) The solid (I*a*) (2·9 g.) was dissolved in 5% aqueous sodium hydroxide (50 c.c.), and benzoyl chloride (1·4 c.c.) was added dropwise, with stirring. The colourless enol *benzoate* crystallized after a few minutes. The crystals (2·3 g.) were washed thoroughly with water and dried in a vacuum-desiccator (P_2O_5). Recrystallization from acetone afforded prisms, m. p. 130—131° (Found: C, 73·3; H, 6·6. $C_{24}H_{25}O_4N$ requires C, 73·65; H, 6·4%).

(*b*) The oil (I*b*) (2·9 g.) was dissolved in dry pyridine (20 c.c.), and benzoyl chloride (1·4 c.c.) was added dropwise, with stirring. The mixture was kept at 20° for 24 hr., then poured into ice-water (40 c.c.). The crude enol benzoate which separated slowly (2·1 g.) was recrystallized four times from acetone, affording colourless prisms, m. p. 117—119° (Found: C, 73·45; H, 6·0%). The mixed m. p. with the enol benzoate, m. p. 130—131°, was 100—110°.

We thank Messrs. R. G. J. Miller and H. A. Willis of Imperial Chemical Industries Limited, Plastics Division, for the spectral measurements and discussion on their interpretation.

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WELWYN GARDEN CITY, HERTFORDSHIRE.

[*Received, July 28th*, 1955.]

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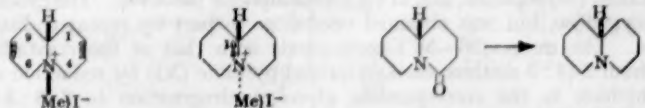
65. *Quinolizines and Quinolizidines. Part I. Reduction of 4-Oxoquinolizidines by Lithium Aluminium Hydride.*

By H. R. LEWIS and C. W. SHOPPEE.

By the action of lithium aluminium hydride, 4-oxoquinolizidine (II) gives quinolizidine (III). Similarly, the (±)-3-ethoxycarbonyl-4-oxoquinolizidines (XII + XIII) give the (±)-3-hydroxymethylquinolizidines [(±)-3-lupinines] (XV + XVI), whilst (±)-1α-methoxycarbonylquinolizidine affords directly (±)-lupinine (as XXVI).

DURING 1953, in an attempt to isolate the *cis*- and the *trans*-quinolizidine methiodides (perhydropyridocoline methiodides) (cf. I*a* and *b*), and to examine their relative stabilities and ease of interconversion by racemisation at $N_{(5)}$, or at $C_{(10)}$,* as a result of activation † by the adjacent positive pole,[3] it was discovered that quinolizidine (III) could be obtained in 70% yield by the action of lithium aluminium hydride in ether or tetrahydrofuran on 4-oxoquinolizidine (II). Thyagarajan [4] states that 4-oxoquinolizidine is unaffected by lithium aluminium hydride, in contradiction of Clemo, Fox, and Raper [5] who, however, give no experimental detail.



(I*a*) (I*b*) (II) (III)

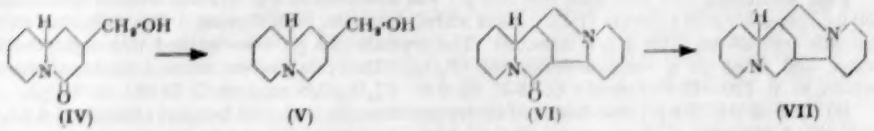
Similar reductions, that of (±)-2-hydroxymethyl-4-oxoquinolizidine (as IV) to (±)-2-lupinine (as V),[6] of (−)-oxosparteine (as VI) to (−)-sparteine (as VII),[7] and of 3-(1-methyl-2-piperidyl)-4-oxoquinolizidine [5] by lithium aluminium hydride, have been recorded, and

* These possibilities have independently been considered by Gellert,[1] who also envisaged the possibility of intermediate fission between the bridgehead carbon and the nitrogen atom followed by recyclization.

† Since this paper was written, an example has been provided by the smooth oxidation of quinolizidinium acetate with mercuric acetate to 2 : 3 : 6 : 7 : 8 : 9-hexahydroquinolizine by Leonard *et al.*[2]

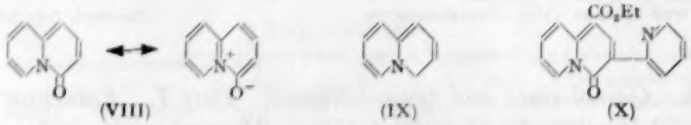
[1] Gellert, *Chem. and Ind.*, 1955, 983.
[2] Leonard, Hay, Fulmer, and Gash, *J. Amer. Chem. Soc.*, 1955, **77**, 439.
[3] Cf. Ingold and Rothstein, *J.*, 1929, 8, and later papers.
[4] Thyagarajan, *Chem. Rev.*, 1954, **54**, 1047.
[5] Clemo, Fox, and Raper, *J.*, 1954, 2693.
[6] Winterfeld and Schneider, *Annalen*, 1953, **581**, 66.
[7] Clemo, Raper, and Short, *Nature*, 1948, **162**, 286; *J.*, 1949, 663.

quantitative reduction of a 6 : 7-dihydro-4-oxoquinolizine derivative by lithium aluminium hydride in refluxing tetrahydrofuran has been observed by Swan.[8]



(IV) (V) (VI) (VII)

In contrast to these reductions, it has been reported by Boekelheide and Lodge [9] that 4-oxoquinolizine (VIII) cannot be reduced to quinolizine (IX) by the use of lithium aluminium hydride. This may be due to the aromatic nature of 4-oxoquinolizine, although a derivative of 4-oxoquinolizine, 1-ethoxycarbonyl-4-oxo-3-2′-pyridylquinolizine (X), has been hydrogenated over copper chromite at 250°/300—350 atm. to a mixture of (±)-sparteine and (±)-*iso*sparteine (as VII).[10]



(VIII) (IX) (X)

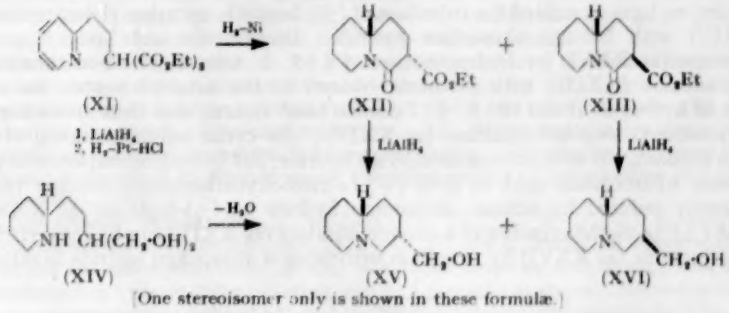
In view of our successful reduction of 4-oxoquinolizidine (II) with lithium aluminium hydride, it was decided to attempt a similar reduction of (±)-3-ethoxycarbonyl-4-oxoquinolizidine (XII + XIII) because Boekelheide and Rothchild [11] have stated that reduction with lithium aluminium hydride in ether gives only 4-oxoquinolizidine (II), and this is quoted in " Organic Reactions," Vol. VI, p. 477. 2-(3 : 3-Diethoxycarbonylpropyl)-pyridine (XI) was hydrogenated with Raney nickel at 145°/200 atm. to a mixture of the two racemates, one form of each of which is represented by [XII; 3-CO_2Et (axial)] and [XIII; 3-CO_2Et (equatorial)]. These compounds are not true β-keto-esters because the presence of the tertiary nitrogen atom adjacent to the 4-carbonyl group, $>\overset{\curvearrowright}{N}\!-\!C\cdot CH\cdot CO_2Et$ (with $C{=}O$), hinders enolisation of the hydrogen atom attached to $C_{(3)}$; thus no colour is developed with ferric chloride, and inversion at $C_{(3)}$ in (XII) to give the more thermodynamically stable isomeride (XIII) does not occur. Reduction with lithium aluminium hydride gave in 70% yield a mixture of (±)-*trans*-3-lupinine (as XV), a structural isomer of the naturally occurring alkaloid (−)-lupinine, and of (±)-*cis*-3-lupinine (as XVI). The product was very difficult to crystallise, but was obtained crystalline in part by repeated distillation in a high vacuum. The m. p. (56—58°) corresponds with that of the crystalline material prepared [12] from 2-(3 : 3-diethoxycarbonylpropyl)pyridine (XI) by reduction with lithium aluminium hydride to the corresponding glycol, hydrogenation to 2-(3 : 3-bishydroxymethyl)piperidine (XIV), and dehydration, or conversion into the dibromide and treatment with sodium acetate.

The structure of our reduction product was confirmed by preparation of a methiodide, picrate, and 3 : 5-dinitrobenzoate, and by oxidation with chromium trioxide to an acid, characterised as the methyl ester. Winterfeld and Heinen [12] state that in their preparation " the formation of the two diastereoisomeric forms of (±)-3-lupinine did not occur." The presence in our reduction product of both (±)-*trans*-3-lupinine (as XV) and (±)-*cis*-3-lupinine (as XVI) is suggested by the infrared absorption spectrum in dilute solution; this shows peaks at 3620 and 3400 cm.$^{-1}$ corresponding with non-bonded and hydrogen-bonded O–H stretching vibrations, the latter being due to an intramolecular $O\text{–}H\leftarrow N\leqslant$ bond

[8] Swan, *J.*, 1949, 1720.
[9] Boekelheide and Lodge, *J. Amer. Chem. Soc.*, 1951, **73**, 3681.
[10] Leonard and Beyler, *ibid.*, 1948, **70**, 2298.
[11] Boekelheide and Rothchild, *ibid.*, 1949, **71**, 879.
[12] Winterfeld and Heinen, *Annalen*, 1953, **578**, 171; 1951, **573**, 85.

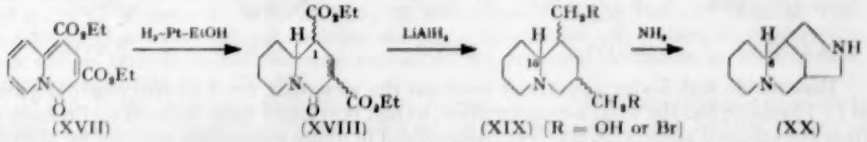
which appears to be possible only if the 3-hydroxymethyl group has the axial configuration (XV).[13] *

The absence of enolisation in the system $>N\cdot CO\cdot\overset{|}{C}H\cdot CO_2Et$, suggested above, finds

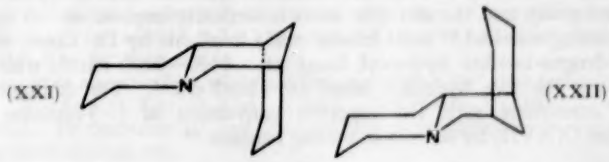


[One stereoisomer only is shown in these formulæ.]

support in the recent synthesis, which also involves reduction of a 4-oxoquinolizidine with lithium aluminium hydride, of (±)-deoxytetrahydrocytisine (XX) by Galinovsky, Vogl, and Moroz : [14] †



In substance (XX), the $-CH_2\cdot NH\cdot CH_2-$ bridge must for steric reasons be attached to the quinolizidine nucleus by bonds which are *cis* to each other; this bridge may be *cis* or *trans* relative to the bridgehead hydrogen atom at position 10 of the quinolizidine nucleus, here position 6 of the tricyclic system. Thus there will be two racemic forms, namely, (*a*) the "*trans*"-form of which one stereoisomer is shown in (XXI), containing three chair conformations, and (*b*) the "*cis*"-form of which one stereoisomer is shown in (XXII), containing



one boat and two chair conformations. Galinovsky *et al.* assumed that their product (XX) contained both racemates, and they describe "the separation of the racemates by means of the dipicrate," although in fact only one crystalline dipicrate was obtained. Predominant or exclusive *cis*-addition of hydrogen in the catalytic reduction of 1 : 3-diethoxycarbonyl-4-oxoquinolizine (XVII) would lead to a single racemate [as XVIII;

* [*Added, December* 21*st*, 1955.] Ratusky *et al.*[13a] prepared the 3-lupinines by another method and separated (±)-*trans*-3-lupinine, m. p. 59° (as XV), from (±)*cis*-3-lupinine, m. p. 30° (as XVI), by chromatography. They assigned configuration on the basis of dipole moments.

† [*Added, December* 21*st*, 1955.] Boekelheide *et al.*[14a] quote a personal communication from Dr. L. Marrian recording the successful reduction of (±)-3-ethoxycarbonyl-4-oxoquinolizidine with lithium aluminium hydride which they have confirmed, without giving experimental details.

[13] Cf. Marion, Ramsay, and R. N. Jones, *J. Amer. Chem. Soc.*, 1951, **73**, 305.

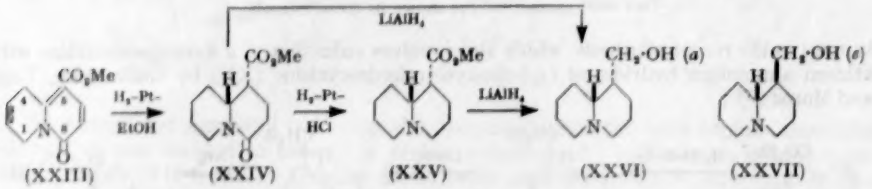
[13a] Ratusky and Šorm, *Coll. Czech. Chem. Comm.*, 1954, **19**, 340; Ratusky, Reiser and Šorm, *ibid.*, 1955, **20**, 798.

[14] Galinovsky, Vogl, and Moroz, *Monatsh.*, 1952, **83**, 246.

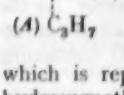
[14a] Boekelheide, Linn, O'Grady, and Lamborg, *J. Amer. Chem. Soc.*, 1953, **75**, 3244.

1α : 3α-CO_2Et (diaxial)] in which enolisation and inversion to the more thermodynamically stable equatorial configuration at position 3 do not occur; clearly, the primary alcohol or alkyl bromide groups (XIX: R = OH or Br) must be *cis*-related for cyclisation, and appear to possess the diaxial α-configuration (cf. XXI).

Finally, we have examined the reduction of (±)-1α-methoxycarbonyl-4-oxoquinolizidine (as XXIV) with lithium aluminium hydride. Boekelheide and Lodge [9] synthesised (±)-lupinine (as XXVI) by hydrogenation of 1 : 2 : 3 : 4-tetrahydro-5-methoxycarbonyl-8-oxoquinolizine (XXIII) with platinum–ethanol to the octahydro-ester, ensuring *cis*-addition of hydrogen at the 10 : 5 : 6 : 7-double-bond system, and thus producing (±)-1α-methoxycarbonyl-4-oxoquinolizidine (as XXIV); the cyclic amide grouping of (XXIV) was then reduced, not with lithium aluminium hydride, but by hydrogenation with platinum in aqueous hydrochloric acid to give (±)-1α-methoxycarbonylquinolizidine (as XXV), subsequently reduced by lithium aluminium hydride to (±)-lupinine (as XXVI). We find that (±)-1α-methoxycarbonyl-4-oxoquinolizidine (as XXIV) can be converted directly into (±)-lupinine (as XXVI) by reduction with lithium aluminium hydride in ether.



Boekelheide and Lodge's synthesis confirms the view that the 1-hydroxymethyl group in (±)-lupinine has the axial α-conformation, as had previously been deduced by Cookson [15] from the infrared absorption spectrum determined in dilute chloroform solution by Marion, Ramsay, and R. N. Jones.[13] Cookson also deduced that the absolute configuration of (−)-lupinine is correctly given by (XXVI) from its conversion by Karrer, Canal, Zohner, and Widner [16] into a 4-methylnonane, $[\alpha]_D$ −1·3°, corresponding with optically pure 4-methylnonane (*A*), $[\alpha]_D$ −1·7°. This assignment is confirmed by examination of the infrared spectrum in dilute carbon disulphide solution of (+)-*epi*lupinine, the absolute configuration of which is represented by (XXVII), in which interaction between the equatorial 1β-hydroxymethyl group and the nitrogen atom is sterically impossible. A specimen of this naturally occurring alkaloid,[17] most kindly made available by Dr. Crow, showed an intermolecular hydrogen-bonded hydroxyl band at ~3400—3200 cm.$^{-1}$, which vanished on dilution, leaving the free hydroxyl band at ~3650 cm.$^{-1}$. The configurations (XXVI, XXVII) are consistent with the reported conversion of (−)-lupinine (XXVI) into (+)-*epi*lupinine (XXVII) by sodium in boiling benzene.[18]



Experimental

For general experimental directions see *J.*, 1955, 2876. The infrared spectrum was determined in CS_2 on a Perkin-Elmer double-beam instrument.

Quinolizidine (III).—(*a*) A solution of lithium aluminium hydride (1 g.) in ether (30 c.c.) was prepared by stirring and refluxing for 2 hr. in a 3-necked flask equipped with an efficient reflux condenser fitted with a calcium chloride tube. The middle neck was equipped with a stirrer (fitted with nichrome wire links) connected through a single-surface condenser to a metal stirrer-head and overhead electric motor. This arrangement obviated the use of the rather inconvenient mercury-seal apparatus. To this solution was added tetrahydrofuran (200 c.c.; purified by distillation over sodium) and the mixture stirred and refluxed for 10 min. 4-Oxoquinolizidine [11] (II) (2·3 g.), dissolved in purified tetrahydrofuran (100 c.c.), was added slowly

[13] Cookson, *Chem. and Ind.*, 1953, 337.
[16] Karrer, Canal, Zohner, and Widner, *Helv. Chim. Acta*, 1928, **11**, 1062.
[17] Crow and Riggs, *Austral. J. Chem.*, 1955, **8**, 136.
[18] Krieg, Diss., Marburg, 1928; cf. Clemo and Rudinger, *J.*, 1951, 2714.

with stirring and the mixture stirred and refluxed for 2 hr. Most of the ether and tetrahydrofuran were removed in a vacuum, and water added cautiously to the residue, which was then made strongly alkaline with 2N-potassium hydroxide. The mixture was extracted thrice with ether, and the combined ethereal extracts were dried and evaporated. The residue (1·7 g.) was distilled to give quinolizidine, b. p. 162°/24 mm. (1·45 g., 69%), identified as the hydrochloride, m. p. 260°, picrate, m. p. 199—200° (Galinovsky and Stern [18] give m. p. 199—200°), and methiodide, m. p. 331—332° (decomp.) (lit.,[19] m. p. 333° (decomp.)].

(*b*) A solution of 4-oxoquinolizidine (2·9 g.) in dry ether (40 c.c.) was added dropwise with stirring to a solution of lithium aluminium hydride (1·2 g.) in ether (60 c.c.) prepared as above, and the mixture set aside and then refluxed for 2½ hr. Water was added dropwise with stirring, and the alumina filtered off and washed with ether. The filtrate was made strongly alkaline with 2N-potassium hydroxide and extracted thrice with ether. The combined ethereal extracts were dried and evaporated, to give an almost colourless residue of quinolizidine (2·0 g., 76%) (picrate, m. p. 197—198°).

(±)-3-*Hydroxymethylquinolizidine* [(±)-3-*Lupinine*] (XV + XVI).—(*a*) A solution of (±)-3-ethoxycarbonyl-4-oxoquinolizidine [11] (XII + XIII) (4·6 g., giving no colour with ferric chloride) in purified tetrahydrofuran (280 c.c.) was added dropwise with stirring to a solution of lithium aluminium hydride (2·0 g.) in ether (500 c.c.) prepared as above. Ether was removed until the vapour temperature reached 62°, and the residual solution was refluxed for 3 hr. After cooling, water was added and the mixture kept overnight. The liquid was decanted and the alumina was washed with ether. The washings and solution were evaporated in a vacuum to small bulk and extracted thrice with ether, the combined ethereal extracts dried and evaporated, and the residue was distilled, to give (±)-3-hydroxymethylquinolizidine, b. p. 97°/0·15 mm. (2·7 g., 70%) (Found: C, 69·3; H, 11·1; N, 8·05. Calc. for $C_{10}H_{19}ON$: C, 71·0; H, 11·2; N, 8·3%). It was very difficult to obtain the product crystalline with a sharp m. p., since it is very soluble both in organic solvents and in water; repeated distillation at 97°/0·15 mm. finally gave crystals, m. p. 57—58°.

(*b*) (Cf. Boekelheide and Rothchild.[11]) A solution of (±)-3-ethoxycarbonyl-4-oxoquinolizidine (5 g.) in dry ether (30 c.c.) was added to one of lithium aluminium hydride (2·1 g.) in ether (150 c.c.) (prepared as above) and refluxed for 1 hr.; working up as in (*a*) gave (±)-3-hydroxymethylquinolizidine (0·6 g., 17·6%), b. p. 138°/mm.

(*c*) (±)-3-Ethoxycarbonyl-4-oxoquinolizidine (4·4 g.) in dry ether (125 c.c.) was added to lithium aluminium hydride (2·2 g.) in ether (150 c.c.) (prepared as above) at 0°, and the whole left overnight, then refluxed for 3 hr. Ethanol (25 c.c.) and then water (10 c.c.) were added dropwise with stirring at 0°. The alumina was filtered off and extracted thrice with hot ethanol. The combined ethanolic solutions were evaporated and made acid to Congo-red with 5N-hydrochloric acid. The aqueous solution was extracted twice with ether, made strongly alkaline with 2N-potassium hydroxide, and extracted four times with ether. The ethereal extracts were dried and evaporated. The residue (2·7 g.) was distilled, to give (±)-3-hydroxymethylquinolizidine (2·4 g., 73%), b. p. 98°/0·15 mm.

Preparation (*a*) gave a methiodide, white needles, m. p. 249—250° after recrystallisation from ethanol (Found: C, 42·3; H, 7·3; N, 4·35; I, 40·3. Calc. for $C_{11}H_{22}ONI$: C, 42·4; H, 7·1; N, 4·5; I, 40·8%). Preparations (*b*) and (*c*) gave this methiodide, m. p. and mixed m. p. 244—246° [with methiodide of (*a*)].

Preparation (*a*) gave a picrate, m. p. 126—127°, after recrystallisation from ethanol (Found: C, 48·27; H, 5·4; N, 16·4. Calc. for $C_{16}H_{22}O_8N_4$: C, 48·24; H, 5·5; N, 14·0%). Preparations (*a*), (*b*), and (*c*) reacted vigorously with acetyl chloride, hydrogen chloride being evolved.

Winterfeld and Heinen [19] gave the following m. p.s: (±)-3-hydroxymethylquinolizidine, m. p. 57·5—58° (b. p. 60—80°/0·010 mm.); picrate, m. p. 140—141·5°; methiodide, m. p. 254—256° (decomp.)].

(±)-3-*Quinolizidylmethyl* 3 : 5-*Dinitrobenzoate*.—(±)-3-Hydroxymethylquinolizidine 204 mg.) was heated under reflux with 3 : 5-dinitrobenzoyl chloride (180 mg.) in benzene (20 c.c.) for 2 hr. and left overnight at 15°. A small amount of a cream-coloured precipitate (probably the hydrochloride of the dinitrobenzoate) was filtered off and washed with benzene; the filtrate was shaken with 4N-sodium hydroxide (10 c.c.), then with water (10 c.c.). After drying, the benzene was removed in a vacuum, and ethanol (1·5 c.c.) added to the residue; after cooling at 0° for 2 hr., the product was filtered off and dried; recrystallisation from ethanol gave (±)-3-*quinolizidylmethyl* 3 : 5-*dinitrobenzoate*, m. p. 108—109° [Found (after drying at 60°/0·02 mm. for 2 hr.): C, 56·1; H, 5·6; N, 11·8. $C_{17}H_{21}O_6N_3$ requires C, 56·2; H, 5·8; N, 11·6%].

[18] Galinovsky and Stern, *Ber.*, 1943, **76**, 1034.

(±)-3-*Carboxyquinolizidine*.—(±)-3-Hydroxymethylquinolizidine (1·21 g.) in sulphuric acid (435 mg.) and water (2·5 c.c.) was mixed with chromium trioxide (1·2 g.) in sulphuric acid (1·74 g.) and water (25 c.c.) at 15°, kept for 1 hr. at 15°, and heated on the water-bath for a further 45 min. Sulphur dioxide was then passed into the solution, which was heated to the b. p. and made alkaline to litmus with aqueous ammonia; excess of ammonia was boiled off, and chromic hydroxide filtered off, and washed twice with boiled water. The combined filtrates were evaporated in a vacuum, and the residue was extracted with boiling ethanol. Evaporation of the extract in a vacuum gave a brown gum, which was suspended in dry acetone and stirred whilst absolute ethanol was added dropwise. In this way, (±)-3-*carboxyquinolizidine* was obtained as an almost colourless powder (A) (50 mg.; m. p. 197—199°), which was purified by sublimation at 110°/0·01 mm. to give amorphous material, m. p. 206° (rapid heating; with slower heating, sintering takes place over a wide range of temperature, although the final m. p. is the same). On account of the extremely hygroscopic nature of this material [cf. lupinic acid (1-carboxyquinolizidine)[20]] a satisfactory analysis could only be obtained after drying at 40°/0·02 mm. (Found: C, 65·3; H, 9·3; N, 7·3. $C_{10}H_{17}O_2N$ requires C, 65·6; H, 9·3; N, 7·6%).

(±)-3-*Methoxycarbonylquinolizidine*.—The filtrate from (A) above was evaporated under reduced pressure, the residue, after drying at 40°/0·02 mm., was dissolved in methanol, and the solution saturated with dry hydrogen chloride and refluxed for 45 min. After evaporation in a vacuum, a little water was added, and the solution made alkaline with potassium carbonate and extracted with ether. The ethereal extract was dried and evaporated, and the residue distilled, to yield (±)-3-*methoxycarbonylquinolizidine*, b. p. 85°/0·6 mm. [795 mg.; 57%, based on (±)-3-hydroxymethylquinolizidine)] (Found: C, 67·2; H, 8·8; N, 7·2. $C_{11}H_{19}O_2N$ requires C, 67·0; H, 9·6; N, 7·1%).

This ester (404 mg.) was refluxed with methyl iodide (1·15 g.) in dry methanol (8 c.c.) for 1 hr. The *methiodide* (525 mg., 76%) was precipitated with ether (m. p. 177—179°, with sintering from 169°) and refluxed in dry acetone (30 c.c.) for 15 min. The undissolved material (m. p. 220°) was filtered off and recrystallised from ether–ethanol, the m. p. rising to 230° (Found: C, 42·8; H, 6·3; N, 4·3. $C_{12}H_{22}O_2NI$ requires C, 42·5; H, 6·5; N, 4·1%). This methiodide was crystalline.

The acetone solution was concentrated and kept at 0° for 3 hr. The resulting precipitate was filtered off (m. p. 187—188°) and recrystallised from dry acetone. The m. p. of this amorphous material was thereby unaltered (Found: C, 42·4; H, 6·5; N, 3·8%).

A mixture of the two methiodides gave a double m. p. 187—189° and 202—207°.

(±)-*Lupinine* (XXVI).—A solution of (±)-1α-methoxycarbonyl-4-oxoquinolizidine[9] (XXIV) (450 mg.) in dry ether (12 c.c.) was added dropwise with stirring to one of lithium aluminium hydride (300 mg.) in ether (20 c.c.) (prepared as above), and the mixture left overnight, then refluxed for 2 hr. Water was added dropwise with stirring, and the alumina filtered off and extracted thrice with hot ethanol. The combined ethanolic solutions were evaporated and made acid to Congo-red with 5N-hydrochloric acid. The aqueous solution was extracted twice with ether, made strongly alkaline with 2N-potassium hydroxide, and extracted thrice with ether. The combined ethereal extracts were dried, and evaporated, leaving a residue (180 mg., 50%) of (±)-lupinine. A methiodide was obtained, having m. p. 288—289° (decomp.) after recrystallisation from absolute ethanol [Boekelheide and Lodge[9] give m. p. 298—301° (decomp.); Clemo, Morgan, and Raper[21] give m. p. 303° (decomp.).] (Found: C, 42·4; H, 7·0; N, 4·8. Calc. for $C_{11}H_{22}ONI$: C, 42·4; H, 7·1; N, 4·5%).

One of us (H. R. L.) acknowledges an award by the Monmouth Local Education Authority. We thank Glaxo Laboratories Ltd. for the determination of the infrared spectrum.

The University of Wales,
University College of Swansea.

[*Received, May 27th*, 1955.]

[20] Willstätter and Fourneau, *Ber.*, 1902, **35**, 1914.
[21] Clemo, Morgan, and Raper, *J.*, 1937, 965; 1938, 1574.

66. *The Formation and Reductive Scission of Bis-compounds from Enols.*

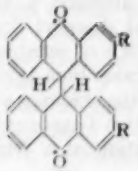
By William Bradley and Leonard J. Watkinson.

On being heated with azobenzene phenols may undergo substitution or self-union with loss of hydrogen (either one atom or two atoms per mol.). Anthrone gives 9 : 9′-dihydro-9 : 9′-dianthrone, 2-methyl-1-naphthol affords 3 : 3′-dimethyldi-1-naphthyl-4 : 4′-quinone, and α-naphthol yields 2-anilino-1 : 4-naphthaquinone 4-anil. 4-Methyl-1-naphthol gives the same anil and in addition 1 : 2-di-(3-anilino-1 : 4-dihydro-4-oxo-1-naphthylidene)ethane. Analogous compounds result by the use of 3 : 3′-dimethyl- and 3 : 3′-dibromo-azobenzene. With dilute nitric acid the ethane derivative gives 1 : 2-di-(1 : 4-dihydro-3-hydroxy-4-oxo-1-naphthylidene)ethane and this has been derived also from 4-methyl-1 : 2-naphthaquinone.

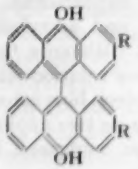
1 : 1 : 2 : 2-Tetrabenzoylethane is reduced to dibenzoylmethane by magnesium in hot pyridine or aqueous pyridine. Amongst analogous compounds only 1 : 2-dibenzoyl-1 : 2-di-*p*-toluoylethane behaves similarly; others afford furan derivatives or do not react. Magnesium subiodide also gives furans, but reductive fission is not observed either with this reagent or with Raney nickel and hydrogen.

It has generally been held [1, 2] that the self-union of phenols begins with the transfer of hydroxylic hydrogen from the phenol to the oxidant, the resulting aryloxy-radicals rearranging and then uniting through carbon. The conditions under which the transfer of hydrogen occurs vary with the oxidant, and for this reason it seemed of interest to study the process of self-union by using aromatic azo-compounds. It was believed that azo-compounds would function solely as neutral, un-ionised hydrogen acceptors, and that their use would enable a simple view of the self-union process to be put forward. Experiment showed that by-products were usually formed, however, and that in some instances the reaction was complex.

Although most azo-compounds are reduced with ease the literature records few examples of their use as hydrogen acceptors. Quinol and diethyl azodicarboxylate afford benzoquinone and diethyl hydrazinedicarboxylate,[3] 2 : 7-dibromo-9-hydroxyfluorene and azobenzene give 2 : 7-dibromofluorenone,[4] and 3-methyl-1-phenylpyrazol-5-one yields di-(3-methyl-1-phenylpyrazol-5-on-4-yl) on being heated with azobenzene.[5] In the present investigation it has been found that anthrone readily yields dianthron-9-yl (I; R = H), together with aniline and hydrazobenzene (identified as benzidine) on being heated with azo-



(I)



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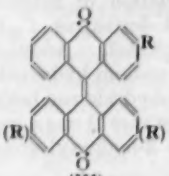


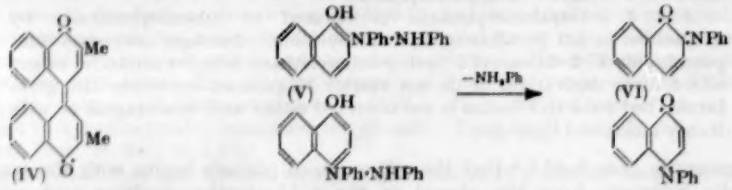
(III)

benzene, but that dianthron-9-yl is stable towards this reagent. Self-union as a result of dehydrogenation with azobenzene appears thus as a property of enolic forms and this accords with the results of Barnett, Cook, and Matthews [1] who employed other oxidants. 3-Chloroanthr-10-one is dehydrogenated, more rapidly than anthrone, to 3 : 3′-dichlorodianthron-9-yl (I; R = Cl); this too was stable. Similar results were obtained on using 3 : 3′-dimethylazobenzene. When the azo-compounds were used in large excess, azobenzene and its

[1] Barnett, Cook, and Matthews, *J.*, 1923, 1994.
[2] Cosgrove and Waters, *J.*, 1951, 388.
[3] Diels and Fritzsche, *Ber.*, 1911, **44**, 3018.
[4] Pinck and Hilbert, *J. Amer. Chem. Soc.*, 1946, **68**, 2740.
[5] Passerini and Losco, *Gazzetta*, 1938, **68**, 485.

dimethyl derivative dehydrogenated anthrone at about the same rate; with a smaller excess the rate was faster with the latter, possibly because the product was less soluble in this medium. 10 : 10′-Dihydroxydi-9-anthryl (II; R = H) yielded dianthron-9-ylidene (III; R = H), anthrone, and anthraquinone on being heated with azobenzene at 180°, and the same products resulted in the absence of the azo-compound. The 3 : 3′-dichloro-derivative (II; R = Cl) and azobenzene gave the related dianthronylidene.

2-Methyl-1-naphthol afforded 3 : 3′-dimethyldi-1-naphthyl-4 : 4′-quinone (IV), identical with the product obtained by the use of ferric chloride.[6] With α-naphthol the product was 2-anilino-1 : 4-naphthaquinone 4-anil, identical with the product derived by heating 4-benzeneazo-1-naphthol with aniline and aniline hydrochloride.[7] This derivative probably arose by the addition of α-naphthol to azobenzene, giving one or both of the hydrazines (V), from which aniline was lost, giving one or both of the anils (VI). 2-Anilino-1 : 4-naphthaquinone 4-anil may be assumed to result from (VI) by the addition of aniline and dehydrogenation. A related reaction, the addition of β-naphthylamine to azodicarboxylic

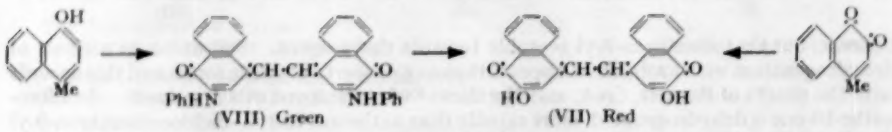


ester to form 2-amino-1-naphthylhydrazine-*NN′*-dicarboxylic ester, has been described by Diels.[8]

4-Methyl-1-naphthol gave 2-anilino-1 : 4-naphthaquinone 4-anil and two other products. That, $C_{34}H_{24}O_2N_2$, formed in larger amount, was green, insoluble in aqueous sodium hydroxide, and stable in hot hydrochloric acid. Oxidation with chromium trioxide gave phthalic acid, and heating with soda-lime gave aniline. Nitric acid (30%) afforded a brown product from which violet-red rhombs were derived by extraction with acetone; these gave a blue solution in sodium hydroxide, and subsequent acidification afforded violet-red plates (B), $C_{22}H_{14}O_4$.

4-Methyl-1-naphthol and 3 : 3′-dibromoazobenzene afforded analogously 2-*m*-bromoanilino-1 : 4-naphthaquinone 4-*m*-bromoanil and a green crystalline compound, $C_{34}H_{22}O_2N_2Br_2$, from which substance B resulted on oxidation with nitric acid. With *m*-azotoluene the products were 2-*m*-toluidino-1 : 4-naphthaquinone 4-3′-methylanil and a green crystalline compound, $C_{36}H_{28}O_2N_2$.

Distillation of substance B gave naphthalene. Methylation afforded a violet-red dimethyl derivative, $C_{22}H_{12}O_2(OMe)_2$, and acetylation a violet-red diacetyl derivative, $C_{22}H_{12}O_2(OAc)_2$. Addition of sodium dithionite to the blue solution of substance B in aqueous sodium hydroxide gave a yellow solution which rapidly became blue again in air. Acetic anhydride and boric acid gave a deep blue colour. Together, the evidence suggested that substance B was a quinone containing two naphthalene nuclei, two 4-carbonyl groups, and two 3-hydroxyl groups. This was confirmed by the preparation of a tetra-acetyl



derivative, $C_{22}H_{12}(OAc)_4$, on reductive acetylation, and a yellow bisquinoxaline derivative, $C_{34}H_{22}N_4$, with *o*-phenylenediamine. The properties indicated that substance B was 1 : 2-di-(1 : 4-dihydro-3-hydroxy-4-oxonaphthylidene)ethane (VII), and this was confirmed by

[6] Lesser, *Annalen*, 1914, **402**, 44.
[7] Fischer and Hepp, *Ber.*, 1888, **21**, 676.
[8] Diels, *Ber.*, 1922, **55**, 1524.

its catalytic reduction to a tetrahydro-derivative and by a synthesis from 4-methyl-1 : 2-naphthaquinone which yielded substance B on being heated with either azobenzene or alcoholic potassium hydroxide.

With the structure of compound (VII) established, the constitution of the green, crystalline compound which results by the action of azobenzene on 4-methyl-1-naphthol is regarded as 1 : 2-di-(3-anilino-1 : 4-dihydro-4-oxonaphthylidene)ethane (VIII). Analogously, the products obtained from 3 : 3′-dibromo- and 3 : 3′-dimethyl-azobenzene are regarded as the dibromo- and dimethyl derivatives of (VIII), the substituents being in the arylamino-groups. Reductive acetylation of the quinone (VIII) afforded the diacetyl derivative of a dihydro-compound.

In agreement with the constitution (VIII) for the product from 4-methyl-1-naphthol, 2 : 4-dimethyl-1-naphthol did not react with azobenzene, and the results suggest further that with 4-methyl-1-naphthol the 2-position enters into reaction first, probably by the mechanism already suggested.[9]

Like α-naphthol, 4-chloro-1-naphthol affords 2-anilino-1 : 4-naphthaquinone 4-anil with azobenzene, but the products from 4-ethyl-, 2-chloro-, 2-chloro-4-methyl-, and 2 : 4-dichloro-1-naphthol could not be obtained pure. Methyl 1-naphthyl ether did not react. 2-Anilino-1 : 4-naphthaquinone 4-anil has been obtained previously in several related reactions, *e.g.*, by heating 4-methyl-, 4-benzyl-, or 4-diethoxycarbonylmethyl-1 : 2-naphthaquinone with aniline in alcohol.[10] In these examples the 4-substituent is replaced by aniline, and this adds further support to the view [9] that in its reaction with azobenzene 4-methyl-1-naphthol yields 4-methyl-1 : 2-naphthaquinone 2-anil and an equimolecular amount of aniline at a stage preceding the formation of 2-anilino-1 : 4-naphthaquinone 4-anil. The formation of 1 mol. of aniline from 1 mol. each of azobenzene and 4-methyl-1-naphthol was shown in other experiments.

The following observations were made in the course of the work. In the preparation of 3-chloroanthr-10-one by Barnett and Wiltshire's method,[11] the reduction of 2-*p*-chlorobenzoylbenzoic acid by zinc dust and ammonia gave 3-*p*-chlorophenylphthalide as the main product unless the reduction proceeded vigorously.

On being exposed to air and sunlight the dichlorodianthronylidene (III; R = Cl) gave a dichloro*meso*naphthadianthronylidene and hydrogen peroxide, the formation of which was observed earlier [12] as a by-product of the oxidation of helianthrone to *meso*naphthadianthronylidene by means of oxygen and ultraviolet light.

No evidence of self-union was found when several open-chain compounds which were capable of enolisation were heated with azobenzene. Of (*a*) diethyl malonate, (*b*) ethyl acetoacetate, (*c*) diethyl oxaloacetate, (*d*) acetoacetanilide, (*e*) acetylacetone, (*f*) benzoylacetone, and (*g*) dibenzoylmethane, only (*c*), (*d*), and (*e*) reacted readily with azobenzene; in each case aniline was formed. In the presence of pyridine, (*b*) and (*f*) also reduced azobenzene. Homogeneous products were not obtained. Further, tetraethyl 1 : 1 : 2 : 2-ethanetetracarboxylate, diethyl αα′-diacetosuccinate, and its dianilide, diethyl ββ′-diacetyl-αα′-dioxoadipate, 1 : 1 : 2 : 2-tetra-acetylethane, 1 : 2-diacetyl-1 : 2-dibenzoylethane, and 1 : 1 : 2 : 2-tetrabenzoylethane, derived by the self-union of the compounds (*a*)—(*f*), did not give homogeneous products: there was evidence of reaction, exception in the first case, and again the formation of aniline was more marked in the presence of pyridine.

Neither 1 : 9-pyrazoloanthrone nor *meso*benzanthrone undergoes self-union on being heated with azobenzene at 180°, although the reaction occurs readily at room temperature with *meso*benzanthrone and sodioaniline,[13] and at 140—160° with 1 : 9-pyrazoloanthrone and alcoholic potassium hydroxide.[14]

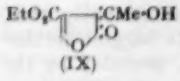
Hitherto no self-union of this type has been reversed. We have now found that 1 : 1 : 2 : 2-tetrabenzoylethane can be reduced to dibenzoylmethane in 8% yield by means of magnesium and pyridine or aqueous pyridine, and it is probable that the reaction is

[9] Bradley and Watkinson, *Chem. and Ind.*, 1954, 1482.
[10] Fieser and Bradsher, *J. Amer. Chem. Soc.*, 1939, **61**, 417.
[11] Barnett and Wiltshire, *J.*, 1928, 1822.
[12] Brockmann and Muhlman, *Ber.*, 1949, **82**, 348.
[13] Bradley and Sutcliffe, *J.*, 1954, 708.
[14] Mayer and Heil, *Chem.-Ztg. Fortschrittber.*, 1929, **56**; G.P. 255,641.

analogous to the reduction of *p*-benzoquinone to quinol, the metal becoming attached to carbonyl oxygen at the first stage. The more usual course of reaction, the formation of a pinacol,[15] is hindered in the present example because of steric considerations.

$$(\cdot CHBz\cdot COPh)_2 \xrightarrow{Mg} (\cdot CHBz\cdot CPh:OMg_{\frac{1}{2}})_2 \longrightarrow 2CHBz{:}CPh\cdot OMg_{\frac{1}{2}} \longrightarrow 2CH_2Bz_2$$

The reaction is not general. Tetramethyl ethane-1 : 1 : 2 : 2-tetracarboxylate did not react with magnesium; 1 : 1 : 2 : 2-tetra-acetylethane formed a stable magnesium enolate. No fission was observed with 1 : 2-dibenzoyl-1 : 2-di-*p*-chlorobenzoyl- or 1 : 2-di-*p*-anisoyl-1 : 2-dibenzoyl-ethane, but 1 : 2-dibenzoyl-1 : 2-di-*p*-toluoylethane afforded a product which gave a copper derivative having approximately the same m. p. as copper ω-*p*-toluoylacetophenone. Diethyl αα-diacetylsuccinate gave ethyl 2 : 3-dihydro-3-1′-hydroxyethylidene-2-oxofuran-4-carboxylate (IX), with cyclisation and elimination of alcohol.


(IX)

Gomberg and Bachmann [16] have shown that the system Mg + MgI_2 reacts with ketones to give ketyls, which then dimerise to pinacols. With this reagent 1 : 1 : 2 : 2-tetrabenzoylethane affords 3 : 4-dibenzoyl-2 : 5-diphenylfuran, and 1 : 1 : 2 : 2-tetra-acetylethane gives correspondingly 3 : 4-diacetyl-2 : 5-dimethylfuran, the main reaction being neither pinacol-formation nor reductive scission but the elimination of water. Neither 1 : 2-diacetyl-1 : 2-dibenzoylethane nor 1 : 1 : 2 : 2-tetra(ethoxycarbonyl)ethane was cleaved by this reagent. None of the tetra-acylethanes afforded diacylmethanes with Raney nickel and hydrogen.

Experimental

Dianthron-9-yl.—Azobenzene (0·9 g.) and anthrone (3·8 g.; m. p. 153—154°) were melted together at 160—170°. In a few minutes crystals separated and after 15 min. the suspension was cooled and extracted with alcohol (3 × 15 c.c.). The extract was evaporated, and the resulting solid was ground and kept in contact with concentrated hydrochloric acid (20 c.c.) for 20 min. The acid solution was filtered and mixed with anhydrous sodium sulphate (3 g.) dissolved in a small volume of water, and the solid which formed was collected. After being dried the residue was extracted with chloroform; a white insoluble solid remained which gave benzidine with sodium hydroxide. The chloroform extract contained azobenzene and dianthron-9-yl, m. p. and mixed m. p. *ca.* 255°; acetylation gave a derivative, m. p. 278—281° (10 : 10′-diacetoxydi-9-anthryl prepared by Barnett and Matthews's method,[17] had m. p. 279—282°).

Azobenzene (3·64 g.) and anthrone (0·97 g.), heated for 4 hr. at 95—100°, gave dianthron-9-yl (80%). When azobenzene (0·5 g.) and anthrone (3 g.) were heated for 4 hr. at 180° in the absence of light and air, the cooled product on extraction with dilute hydrochloric acid afforded a solution from which 2 : 4 : 6-tribromoaniline (1·2 g.) separated on the addition of bromine water.

Dianthron-9-yl was recovered unaltered after being further heated at 180° with azobenzene.

Azobenzene (2 g.) and 10 : 10′-dihydroxydi-9-anthryl (1 g.) reacted at 180° in the dark and *in vacuo* during 4 hr. to give aniline and dianthron-9-ylidene, and at this temperature the diol alone decomposed. Diol prepared by Barnett and Matthews's method [17] gave anthrone and dianthron-9-ylidene. Diol obtained by Meyer's method,[18] when heated in carbon dioxide at 180°, gave anthraquinone and dianthron-9-ylidene.

3-Chloroanthr-10-one.—Zinc dust (150 g.) was added slowly and with cooling to a stirred suspension of *o-p*′-chlorobenzoylbenzoic acid (50 g.) in water (150 c.c.) and ammonia (300 c.c.; *d* 0·880). The suspension cleared and, when the addition of zinc dust was complete, a concentrated solution (5 c.c.) of copper sulphate was added; the reactants were then stirred under reflux on the water-bath. It was necessary to raise the temperature during 2 hr. because of the vigorous foaming which occurred at 70°; thereafter heating was continued for 36 hr. The reduction was complete when a portion of the product precipitated by the addition of hydrochloric acid dissolved completely in aqueous sodium carbonate. The main portion was then

[15] Bachmann, *J. Amer. Chem. Soc.*, 1944, **55**, 1179.
[16] Gomberg and Bachmann, *ibid.*, 1927, **49**, 236.
[17] Barnett and Matthews, *J.*, 1923, 380.
[18] Meyer, *Ber.*, 1909, **42**, 143.

filtered; addition of concentrated hydrochloric acid to the filtrate precipitated 2-carboxy-4'-chlorodiphenylmethane. The residue was extracted with hot dilute aqueous ammonia, and the filtered extracts were combined and acidified. The total yield of the reduced acid was 40 g. After being washed with water and crystallised from alcohol the acid had m. p. 130—132° (Barnett and Wiltshire [11] give m. p. 132°).

Cyclisation gave 3-chloroanthr-10-one, m. p. 154—155°, and this on acetylation afforded 9-acetoxy-2-chloroanthracene, m. p. 142—143° (Barnett and Wiltshire [11] record m. p.s 155° and 143°).

3-p-*Chlorophenylphthalide.*—When in the preceding preparation zinc powder was used instead of dust, reaction was less vigorous and the *phthalide* crystallised from alcohol in colourless needles, m. p. 124° (Found: Cl, 14·3. $C_{14}H_9O_2Cl$ requires Cl, 14·5%). The same compound was also obtained, together with impure 2-carboxy-4'-chlorodiphenylmethane, by the reduction of *o-p*-chlorobenzoylbenzoic acid by the method of B.I.O.S. Report No. 1493, p. 47. The phthalide is neutral but combines slowly with warm aqueous sodium hydroxide. Vigorous reduction with zinc dust, ammonia, and aqueous sodium hydroxide gave 2-carboxy-4'-chlorodiphenylmethane.

3 : 3'-*Dichlorodianthron*-9-*ylidene.*—Azobenzene (3·6 g.) and 3-chloroanthr-10-one (1 g.) were heated for 3 hr. at 100° and the product was worked up as with anthrone. The yield of dianthronylidene was 0·85 g.; it was characterised by heating it with acetic anhydride and pyridine to give 10 : 10'-diacetoxy-3 : 3'-dichlorodi-9-anthryl, m. p. and mixed m. p. 308° (Found: C, 70·8; H, 3·7. Calc. for $C_{32}H_{22}O_4Cl_2$: C, 71·0; H, 4·1%). When azobenzene (0·8 g.) and 3-chloroanthr-10-one (2 g.) were heated under the same conditions and the cooled product was extracted with dilute hydrochloric acid, addition of concentrated hydrochloric acid to the filtered extract gave benzidine, isolated as the sulphate (1 g.).

3 : 3'-Dichloro-10 : 10'-dihydroxydi-9-anthryl (1 g.) gave 3 : 3'(or 3 : 6')-dichlorodianthron-9-ylidene on being heated for 4 hr. at 180° *in vacuo* with azobenzene (3·6 g.). Neither 3 : 3'(or 3 : 6')-dichlorodianthronylidene nor 3 : 3'-dichlorohelianthrone reacted with azobenzene under these conditions.

Azobenzene and 3 : 3'-*Dimethylazobenzene as Dehydrogenating Agents.*—(*a*) Anthrone (0·5 g.) and 3 : 3'-dimethylazobenzene (2·2 g.) were heated together at 100° for 1·5 hr. The product was then cooled and extracted with acetone (15 c.c.); the residue of dianthronyl weighed 0·16 g. Use of an equivalent amount of azobenzene (1·82 g.) gave 0·06 g.

When 0·095 g. of anthrone was used and heating was for 1 hr. the yields of dianthronyl were 0·037 g. on use of azobenzene and 0·041 g. with its 3 : 3'-dimethyl derivative.

(*b*) 3-Chloroanthrone (0·5 g.) was kept at 100° with azobenzene (1·82 g.). Precipitation of 3 : 3'-dichlorodi-9-anthronyl occurred in 5 min.; after 1·5 hr. the yield was 0·28 g. 3 : 3'-Dimethylazobenzene under the same conditions gave 0·29 g.

Action of Light on 3 : 3'(*or* 3 : 6')-*Dichlorodianthronylidene.*—A 0·1% solution of the dichlorodianthronylidene was introduced into 12 tubes which were then lightly stoppered. Six were exposed to sunlight and the remainder were kept in the dark. After 30 min. 5 c.c. of solution from an exposed tube were shaken with water (10 c.c.), and the aqueous solution was shaken with 10% potassium iodide solution (1 c.c.), 2N-sulphuric acid (1 c.c.), and starch solution (0·5 c.c.); a blue colour developed after 2 min. Similar treatment of a non-irradiated solution gave no evidence of hydrogen peroxide. The intensity of the blue colour increased up to 6·5 hours' exposure and was then constant for a further 14 hours' exposure.

Action of Azobenzene on α-Naphthol.—Azobenzene (1·5 g.) and α-naphthol (1·4 g.), heated for 9 hr. at 180° in a sealed evacuated tube, afforded a black, viscous mass. This was dissolved in benzene and chromatographed on alumina. The lowest band (azobenzene) was removed and the next was eluted and re-chromatographed; separation into two bands occurred. The lower was eluted and the solute recovered and crystallised from light petroleum (b. p. 60—80°). Red needles (0·25 g.), m. p. 182°, were obtained which did not depress the m. p. of 2-anilino-1 : 4-naphthaquinone 4-anil prepared from 4-phenylazo-1-naphthol, aniline, and aniline hydrochloride. The absorption spectra of the two products in "AnalaR" concentrated sulphuric acid were identical ($\lambda_{max.}$ 261·5, 277·5, 360, 530 mμ).

3 : 3'-*Dimethyldi*-1-*naphthyl*-4 : 4'-*quinone.*—2-Methyl-1-nitronaphthalene [10] was reduced and the derived amine was diazotized and converted into 2-methyl-1-naphthol by Lesser's method.[6] 2-Methyl-1-naphthol (0·15 g.) and azobenzene (0·18 g.) were heated for 10 hr. at 160° *in vacuo*. The cooled product was extracted with light petroleum (b. p. 40—60°); the grey

[10] Fierz-David, *Helv. Chim. Acta*, 1937, **20**, 1027.

powder [0·13 g., m. p. 250° (decomp.)] which remained undissolved showed the same absorption spectrum in " AnalaR " concentrated sulphuric acid as the authentic dinaphthylquinone (IV) (0·001% solutions; a Unicam S.P. 500 Spectrophotometer), *viz.*:

$\lambda_{max.}$ (mμ)	222	245	290	442	662
10^{-3} ε	>50, >50	8·0, 7·0	9·0, 8·0	6·0, 6·5	14·2, 12·5

Reaction of 4-*Methyl*-1-*naphthol with Azobenzene.*—1-Methylnaphthalene was converted into the 4-sulphonic acid by Steige's method,[20] and this into the naphthol according to Fieser and Bradsher.[10] At the final stage it was advantageous to purify the product by short-path distillation (Towers model T 331 still). The molten crude product was degassed at 75° for 2 hr. and then distilled during 2 hr. while the temperature was raised from 80° to 95°. Recrystallisation from ligroin (b. p. 40—60°) gave prisms, m. p. 84—85°, which did not change on storage. 4-Methyl-1-naphthol (3 g.) and azobenzene (3·6 g.) were heated for 12 hr. at 150° in a sealed evacuated tube. The cooled melt was extracted with benzene and the extract separated from the green crystals (1·8 g.) which remained undissolved. The benzene solution was chromatographed on alumina; there resulted a strongly adsorbed, dark band and two others, the lower of which was azobenzene. The middle band on elution with benzene gave dark red material (0·3 g.; m. p. 171—173°) from which was obtained by recrystallisation from light petroleum (b. p. 60—80°) 2-anilino-1 : 4-naphthaquinone 4-anil as red needles, m. p. and mixed m. p. 180—181° (Found: C, 81·3; H, 5·2; N, 8·6. Calc. for $C_{22}H_{16}ON_2$: C, 81·5; H, 4·9; N, 8·7%). The absorption spectra of 0·001% solutions of the two preparations in " AnalaR " concentrated sulphuric acid were identical [$\lambda_{max.}$ 255 (ε 2050), 270 (ε 2200), 360 (ε 1100), 525 mμ (ε 8000).

The green crystals, when extracted for a day with acetone, afforded a soluble, colourless portion (m. p. >360°; 0·2 g.). Further crystallisation of the residue from 1 : 2 : 4-trichlorobenzene gave flat, thin, green needles of 1 : 2-*di*-(3-*anilino*-1 : 4-*dihydro*-4-*oxonaphthylidene*)-*ethane* (A), m. p. >360° (Found: C, 82·8; H, 4·9; N, 6·1. $C_{34}H_{24}O_2N_2$ requires C, 82·9; H, 4·9; N, 5·7%). At all stages of purification the product exhibited a strong bronze reflex.

Reactions of product (*A*). (*a*) The diketone (0·1 g.) was recovered unaltered after being heated in a sealed tube with concentrated hydrochloric acid (10 c.c.) and alcohol (10 c.c.) for 12 hr. at 150°. (*b*) It (2 g.) was stirred into cold dilute nitric acid (20 c.c.; *d* 1·18), then kept overnight; the solid was collected, washed acid-free with water, and added to a solution of sodium dithionite (0·5 g.) and sodium hydroxide (2 g.) in water (50 c.c.); a dark blue solution was formed and from this golden platelets rapidly separated. These were collected, washed with 15% aqueous sodium hydroxide until the filtrate was no longer brown, and then added to water (50 c.c.). The resulting dark blue solution was filtered and then acidified. A red-brown precipitate was formed which on drying and crystallisation from 1 : 2 : 4-trichlorobenzene (1 l.) afforded red-violet, thin plates (0·65 g.), m. p. 345° (decomp.) (Found: C, 76·7; H, 4·0. $C_{28}H_{14}O_4$ requires C, 77·2; H, 4·1%), of 1 : 2-*di*-(1 : 4-*dihydro*-3-*hydroxy*-4-*oxonaphthylidene*)-*ethane* (B); the crystals had a marked greenish-yellow reflex.

Constitution of the ketone (*B*). (*a*) Zinc dust (5 g.) and the product (B) (0·3 g.) in a bent Pyrex tube were covered with zinc dust. On being heated the mixture afforded naphthalene as a sublimate, m. p. and mixed m. p. 80°, unaltered by naphthalene. (*b*) Methylation. Methyl sulphate (0·1 c.c.) was heated with a solution of the product (B) (0·1 g.) in water (8 c.c.) containing sodium hydroxide (0·25 g.) on the water-bath and shaken at intervals for 30 min. during which further methyl sulphate (0·1 c.c.) and 25% sodium hydroxide (0·25 c.c.) were added; the initial blue colour disappeared. The precipitated dimethyl derivative was washed with dilute sodium hydroxide, then water, dried (yield 0·1 g.), and crystallised from *o*-dichlorobenzene (10 c.c.), giving red-violet needles (35 mg.), m. p. 283° (decomp.) [Found: C, 77·4; H, 4·8; OMe, 15·9. $C_{32}H_{18}O_2(OMe)_2$ requires C, 77·8; H, 4·9; OMe, 16·8%]. The *dimethyl compound* is insoluble in dilute aqueous sodium hydroxide but dissolves to a yellow solution on the addition of sodium dithionite. (*c*) Reductive acetylation. The product (B) (0·4 g.) was methylated as in (*b*) and the washed and dried product was dissolved in boiling acetic anhydride (10 c.c.) containing a drop of pyridine. On the addition of zinc dust (1 g.) in small amounts the solution rapidly became pale yellow. It was refluxed for 15 min., then filtered and cooled. The solid which separated was collected and washed with dilute acetic acid and water. The *dimethyl ether diacetate* of the dihydro-compound crystallised from acetic anhydride as pale

[20] Steige, *Helv. Chim. Acta.*, 1930, **13**, 173.

cream-coloured needles, m. p. 291—292° (Found : C, 73·2; H, 5·3. $C_{28}H_{24}O_4$ requires C, 73·6; H, 5·3%). (*d*) Acetylation. Product (B) (0·1 g.), on being boiled for 10 min. with acetic anhydride (2 c.c.) containing a drop of pyridine, changed to red-violet needles. After being cooled, the 1 : 2-*di*-(3-*acetoxy*-1 : 4-*dihydro*-4-*oxonaphthylidene*)*ethane* was collected, washed with benzene, and recrystallised from chlorobenzene. The pure compound had m. p. 260° (decomp.) (Found : C, 73·4; H, 4·3. $C_{32}H_{18}O_6$ requires C, 73·9; H, 4·2%). On being heated with a saturated solution of boric acid in acetic anhydride (2 c.c.), the product (B) (0·05) dissolved to form a deep royal-blue solution from which dark bluish-purple needles separated. (*e*) Zinc dust (1 g.) was added quickly in small successive amounts to a boiling suspension of the product (B) (0·2 g.) in acetic anhydride (5 c.c.) containing a drop of pyridine. The yellow solution was filtered and then kept; a yellow precipitate was collected, washed with dilute acetic acid and water, and crystallised from acetic anhydride. The pale yellow needles of 1 : 2-*di*-(3 : 4-*diacetoxy*-1-*naphthyl*)*ethylene* had m. p. 277—278° [Found : C, 70·3; H, 5·0; *M* (Rast), 460, 520. $C_{30}H_{24}O_8$ requires C, 70·3; H, 4·7%; *M*, 512%). (*f*) *o*-Phenylenediamine (0·5 g.) and product (B) (0·5 g.) were refluxed for 3·5 hr. in 1 : 2 : 4-trichlorobenzene (5 c.c.) containing glacial acetic acid (1 c.c.). Crystals of 1 : 2-*di*-(1 : 2-*benzophenazin*-3-*yl*)*ethane* were formed on cooling; and these were washed with benzene and recrystallised from 1 : 2 : 4-trichlorobenzene as bright yellow needles, m. p. >360° (Found : N, 11·6, 11·7. $C_{34}H_{22}N_4$ requires N, 11·5%). (*g*) Preparation from 4-methyl-1 : 2-naphthaquinone. (i) Azobenzene (1 g.) and 4-methyl-1 : 2-naphthaquinone [10] (0·05 g.; m. p. 108—109°) were heated for 5 hr. at 110° in an evacuated sealed tube. The cooled product was extracted with light petroleum (b. p. 40—60°), then with acetone, and finally the dark brown residue was crystallised from 1 : 2 : 4-trichlorobenzene, giving red-violet needles, m. p. 345° (decomp.), of 1 : 2-di-(1 : 4-dihydro-3-hydroxy-4-oxonaphthylidene)ethane. A 0·001% solution of the present preparation, like one of the product from 4-methyl-1-naphthol and azobenzene, had $\lambda_{max.}$ at 250, 305, 420, and 660 mμ. (ii) An identical product was obtained when 4-methyl-1 : 2-naphthaquinone (0·1 g.) was added to a refluxing solution of potassium hydroxide (1 g.) in ethyl alcohol (5 c.c.) and heated for 30 min. The solution became green immediately and brownish-yellow after 15 min. On addition to water (50 c.c.) a dark blue colour developed. Further addition of hydrochloric acid gave a maroon precipitate; this was washed and dried (0·04 g.). Crystallisation from 1 : 2 : 4-trichlorobenzene gave red-violet needles.

Constitution of product (*A*). (*a*) Chromium trioxide (5 g.) was added gradually during 2 hr. to a stirred suspension of product (A) (1·5 g.) in glacial acetic acid (50 c.c.). After a further 2 hours' boiling the suspension was filtered and the filtrate added to water (200 c.c.) containing concentrated sulphuric acid (2 c.c.). The resulting suspension was heated and stirred on the water-bath, and the brown solid (0·5 g.) was collected. Purification gave white needles, m. p. *ca.* 125° (sublimation), which afforded fluorescein on being heated with resorcinol and sulphuric acid. (*b*) A mixture of zinc dust (10 g.) and product (A) (0·5 g.) was added during 30 min. to refluxing acetic anhydride (50 c.c.). The suspension was then filtered and the filtrate was added to ice. After being kept overnight the pale green, granular precipitate was washed and dried (0·5 g.). Purification from chlorobenzene (charcoal) gave pale cream-coloured crystals, m. p. 274—275° (decomp.) (Found : C, 79·2; H, 5·3; N, 4·65. $C_{34}H_{20}O_4N_2$ requires C, 78·9; H, 5·2; N, 4·8%). (*c*) A mixture of soda-lime (10 g.) and product (A) (1 g.) was heated in a slow current of nitrogen. Aniline distilled; it was collected in water and weighed as 2 : 4 : 6-tribromoaniline (0·5 g., equiv. to aniline, 0·1 g.). In a second experiment the yield of aniline was 0·1 g. from 0·5 g. of product (A).

Formation of Aniline in the Action of Azobenzene on 4-Methyl-1-naphthol.—Azobenzene (3·6 g.) and 4-methyl-1-naphthol (3·2 g.) were heated at 160° for 12 hr. in a sealed evacuated tube. The product was then transferred to a Pozzi–Escott apparatus and steam-distilled. The yield of aniline as determined by titration with acidified bromide–bromate was 1·5 g. The 2 : 4 : 6-tribromoaniline produced in the estimation weighed 5·1 g., equiv. to 1·4 g. of aniline. Repetition of the experiment using azobenzene (7·2 g.) and 4-methyl-1-naphthol (3·2 g.) gave 2·0 g. of aniline (by direct titration), or 1·75 g. of aniline (calc. from the yield of 2 : 4 : 6-tribromoaniline).

Action of 3 : 3′-Dimethylazobenzene on 4-Methyl-1-naphthol.—3 : 3′-Dimethylazobenzene (4·2 g.) and 4-methyl-1-naphthol (3·0 g.) were heated for 12 hr. at 150° in a sealed, evacuated tube, then treated with benzene, giving an insoluble 1 : 2-*di*-(1 : 4-*dihydro*-4-*oxo*-3-*m*-*toluidinonaphthylidene*)*ethane* which crystallised from 1 : 2 : 4-trichlorobenzene in dark green needles (bronze reflex), m. p. >360° (Found : C, 83·0; H, 5·4; N, 5·75. $C_{34}H_{28}O_2N_2$ requires C, 83·0; H, 5·4; N, 5·4%). The benzene solution, chromatographed on alumina, gave two bands; the more mobile contained 3 : 3′-dimethylazobenzene and white material, m. p. >360°; the less

mobile band yielded red needles, m. p. 145°, of 2-m-*toluidino*-1 : 4-*naphthaquinone* 4-3′-*methylanil* (Found : C, 81·7; H, 5·4; N, 8·2. $C_{24}H_{20}ON_2$ requires C, 81·8; H, 5·7; N, 7·95%).

Action of 3 : 3′-*Dibromoazobenzene on* 4-*Methyl*-1-*naphthol*.—3 : 3′-Dibromoazobenzene [21] (3·4 g.), and 4-methyl-1-naphthol (1·6 g.) were treated as in the experiment with the dimethyl analogue. Extraction of the crude product with benzene gave a dark residue (0·9 g.) and a solution (C). The solid was extracted with acetone, and then crystallised (0·5 g.) from 1 : 2 : 4-trichlorobenzene. 1 : 2-*Di*-(3-m-*bromoanilino*-1 : 4-*dihydro*-4-*oxonaphthylidene*)*ethane* is a brownish solid, m. p. >360° (Found : C, 62·7, 63·2; H, 3·5, 3·3; N, 4·1, 3·9; Br, 26·5, 24·8. $C_{34}H_{28}O_2N_2Br_2$ requires C, 62·75; H, 3·4; N, 4·3; Br, 24·6%), which is blue-green in thin layers. Oxidation of 0·5 g. with nitric acid (20 c.c.; *d* 1·18), as in the experiment with the corresponding product from 4-methyl-1-naphthol and azobenzene, gave 1 : 2-di-(1 : 4-dihydro-3-hydroxy-4-oxonaphthylidene)ethane identical with the compound (B) derived from the azobenzene product (A) ($\lambda_{max.}$ at 250, 305, 420, and 660 mμ). Solution (C) was chromatographed on alumina. Two mobile bands were formed, the lower containing 3 : 3′-dibromoazobenzene and white material m. p. >360°. The upper band was eluted; recovery of the dissolved solid and crystallisation from light petroleum (b. p. 40—60°) gave 2-m-*bromoanilino*-1 : 4-*naphthaquinone* 4-3′-*bromoanil* as red needles, m. p. 192° (Found : C, 54·9; H, 3·1; N, 5·7. $C_{22}H_{14}ON_2Br_2$ requires C, 54·8; H, 2·9; N, 5·8%).

Action of Azobenzene on 4-*Chloro*-1-*naphthol*.—After being heated at 150° for 12 hr. in a sealed, evacuated tube azobenzene (3·62 g.) and 4-chloro-1-naphthol (3·56 g.) afforded a black product. This was extracted with light petroleum (b. p. 60—80°) and the soluble portion was chromatographed on alumina. The most mobile band consisted of azobenzene; next followed a red band and this was eluted with light petroleum. The eluate afforded red needles (Found : C, 81·1; H, 5·0; N, 9·0%), m. p. 183° not depressed by 2-anilino-1 : 4-naphthaquinone 4-anil.

Reduction experiments.

In the preparation of *sym.*-tetra-acylethanes from diacylmethanes by the action of iodine on sodio-derivatives in ether it was often advantageous to extract the ether-insoluble part of the product because of the low solubility of many tetra-acylethanes in the medium.

Reduction of 1 : 1 : 2 : 2-*Tetrabenzoylethane*.—(*a*) Magnesium powder (0·1 g.) was heated for 48 hr. at 90—95° with a solution of 1 : 1 : 2 : 2-tetrabenzoylethane [22] (0·8 g.) in pyridine (10 c.c.). The resulting suspension was filtered, and the filtrate was diluted, acidified, and extracted with ether. The extract, washed with water and then shaken with saturated aqueous copper acetate, gave the copper derivative of dibenzoylmethane (0·05), m. p. and mixed m. p. 211°. When the experiment was repeated with the addition of water (2 c.c.) at such a rate as to maintain slow evolution of hydrogen, the same copper derivative (0·06 g.) was obtained.

There was no evidence of fission when 1 : 2-dibenzoyl-1 : 2-di-*p*-chlorobenzoylethane and 1 : 2-di-*p*-anisoyl-1 : 2-dibenzoylethane were treated similarly, but 1 : 2-dibenzoyl-1 : 2-di-*p*-toluoylethane gave 0·04 g. of a *copper derivative*, m. p. *ca.* 230° (decomp.) (of benzoyl-*p*-toluoylmethane), m. p. 236° (decomp.) (Found : C, 71·1; H, 5·0; Cu, 11·8. $C_{32}H_{26}O_4Cu$ requires C, 71·5; H, 4·8; Cu, 11·8%).

(*b*) To a solution of magnesium subiodide, prepared from magnesium (0·1 g.) and iodine (0·25 g.) in benzene (7 c.c.) and ether (3·5 c.c.), was added one of 1 : 1 : 2 : 2-tetrabenzoylethane (0·9 g.) in benzene (60 c.c.), and the mixture was shaken 2 hr. A resultant precipitate was filtered off and the filtrate was shaken with a small volume of dilute sulphuric acid. Evaporation of the benzene–ether solution gave a crystalline residue and this was extracted with a small volume of aqueous methanol or acetone; 1 : 1 : 2 : 2-tetrabenzoylethane remained undissolved. From the extracts needles separated and these afforded 3 : 4-dibenzoyl-2 : 5-diphenylfuran, m. p. and mixed m. p. 141° (Found : C, 84·1; H, 4·4. Calc. for $C_{30}H_{20}O_3$: C, 84·1; H, 4·7%); a further quantity was obtained by ether-extraction of the aqueous acid washings.

1 : 1 : 2 : 2-*Tetra-acetylethane*.—Similar treatment of 1 : 1 : 2 : 2-tetra-acetylethane (1 g.) with magnesium (0·24 g.) and iodine (0·63 g.) in benzene–ether gave a bulky precipitate of the magnesium derivative of the tetraketone. From the benzene–ether solution were obtained unchanged material and 3 : 4-diacetyl-2 : 5-dimethylfuran, m. p. 62—63° (Found : C, 66·8; H, 6·5. Calc. for $C_{10}H_{12}O_3$: C, 66·7; H, 6·7%), identical with the product obtained by the action of sulphuric acid [23] or hydrochloric acid [24] on the tetraketone.

[21] Gabriel, *Ber.*, 1876, **9**, 1407.
[22] Abell, *J.*, 1912, 997.
[23] Mullikan, *Amer. Chem. J.*, 1893, **15**, 532.
[24] Zanetti, *Gazzetta*, 1893, **23**, II, 307.

A solution of hydrazine hydrate (1·2 g.) in glacial acetic acid (5 c.c.) was added with stirring at 0° to one of 3 : 4-diacetyl-2 : 5-dimethylfuran (3·6 g.) in acetic acid (10 c.c.). Water (50 c.c.) and then 4% sodium hydroxide were added until a cream-coloured precipitate resulted. This was collected, washed with a small volume of water, then crystallised twelve times from hot water. The *monohydrazone* formed long needles, m. p. 136—140° (decomp.) (Found : C, 62·2; H, 7·2; N, 14·5. $C_{10}H_{14}O_2N_2$ requires C, 61·9; H, 7·2; N, 14·4%). On being kept for several days the mother-liquors afforded a small quantity of another product, m. p. 244—246° (decomp.) (Found : N, 28·9. $C_{10}H_{14}ON_4$ requires N, 26·9%), which was probably the *dihydrazone*.

Diethyl αα′-Diacetylsuccinate.—Magnesium powder (0·2 g.) was heated for 48 hr. with a solution of diethyl αα′-diacetylsuccinate (0·85 g.) in pyridine (10 c.c.). The colour became light purple-brown, then deep yellow-brown. The filtered solution was mixed with water, acidified, and then extracted with ether. The extract, washed with water, gave a pale yellow-brown crystalline precipitate when it was shaken with saturated cupric acetate solution. The product was washed with water, then ether; crystallised from benzene, it had m. p. 220° (decomp.) (Found : C, 49·4; H, 4·7; Cu, 13·1. Calc. for $C_{20}H_{22}O_{10}Cu$: C, 49·4; H, 4·5; Cu, 13·1%) and was identical with the copper derivative of ethyl 2 : 3-dihydro-3-1′-hydroxyethylidene-2-oxofuran-4-carboxylate. The copper compound decomposed in contact with dilute sulphuric acid to form white needles (from alcohol) of the ester, m. p. 106° (Found : C, 56·7; H, 5·7. Calc. for $C_{10}H_{12}O_5$: C, 56·6; H, 5·7%) not depressed by a sample prepared by heating diethyl αα′-diacetylsuccinate at 170—190°, extraction with dilute alkali, and acidification.[25]

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[*Received, August 16th*, 1955.]

[25] Knorr and Haber, *Ber.*, 1894, **27**, 1159.

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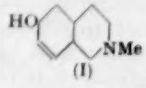
67. *Decahydroisoquinolines and Related Compounds. Part I. Some 6-Oxygenated Derivatives and an Example of Abnormal Ultraviolet Absorption.*

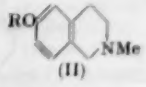
By ALAN MARCHANT and A. R. PINDER.

The synthesis of some reduced 6-oxygenated *iso*quinolines is described. The constitution of the product obtained by the reduction, with sodium and liquid ammonia, and hydrolysis of 1 : 2 : 3 : 4-tetrahydro-6-methoxy-2-methyl*iso*quinoline has been proved by synthesis. This product, 1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-octahydro-2-methyl-6-oxo*iso*quinoline (VI), shows maximal ultraviolet absorption at an abnormally short wavelength.

THE accepted structure of morphine,[1] confirmed by synthesis,[2] contains 1 : 2 : 3 : 4 : 5 : 6 : 9 : 10-octahydro-6-hydroxy-2-methyl*iso*quinoline (I) as one unit.[3] Since little is known of the chemistry of oxygenated octa- and deca-hydro*iso*quinolines, it seemed of interest to investigate the synthesis of such compounds, which may have interesting pharmacological properties.



(I)



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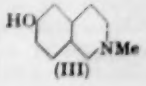


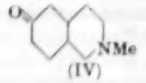
(III)

Only two *Bz*-hydroxydecahydro*iso*quinolines are known. Woodward and Doering [4] prepared decahydro-7-hydroxy-8-methyl*iso*quinoline and 2-acetyldecahydro-8-methyl-7-oxo*iso*quinoline, as intermediates in the synthesis of quinine, and Mannich and Hieronimus,[5] and Boekelheide and Schilling,[6] synthesised decahydro*iso*quinolines with angular hydroxyl substituents.

[1] Gulland and Robinson, *Mem. Manchester Lit. Phil. Soc.*, 1925, **69**, 79.
[2] Gates and Tschudi, *J. Amer. Chem. Soc.*, 1952, **74**, 1109.
[3] Cf. Boekelheide, *ibid.*, 1947, **69**, 790.
[4] Woodward and Doering, *ibid.*, 1944, **66**, 849; 1945, **67**, 860.
[5] Mannich and Hieronimus, *Ber.*, 1942, **75**, 49.
[6] Boekelheide and Schilling, *J. Amer. Chem. Soc.*, 1950, **72**, 712; see also Grewe, Hamann, Jacobsen Nolte, and Riecke, *Annalen*, 1953, **581**, 85.

A convenient approach to 6-oxygenated reduced *iso*quinolines was from 1 : 2 : 3 : 4-tetrahydro-6-methoxy-2-methyl*iso*quinoline (II; R = Me), which was synthesised from *m*-hydroxybenzaldehyde (see p. 329). *O*-Demethylation of this base [7] afforded 1 : 2 : 3 : 4-tetrahydro-6-hydroxy-2-methyl*iso*quinoline (II; R = H), which on hydrogenation in presence of platinum oxide gave decahydro-2-methyl*iso*quinoline, in harmony with Woodward and Doering's observation [4] that 2-acetyl-1 : 2 : 3 : 4-tetrahydro-7-hydroxy-8-methyl*iso*quinoline gave much 2-acetyl-8-methyldecahydro*iso*quinoline under similar conditions.

Use of Raney nickel at high temperature and pressure, however, afforded smoothly an excellent yield of decahydro-6-hydroxy-2-methyl*iso*quinoline (III), without hydrogenolysis, and this on oxidation with chromic acid furnished decahydro-2-methyl-6-oxo*iso*quinoline (IV). Unsuccessful attempts were made to separate the crystalline picrate of this keto-base into *cis*- and *trans*-forms. It seems likely, therefore, that the ketone is stereochemically homogeneous; it is probably the *trans*-form, by analogy with Witkop's observations [8] that the reduction of 2-acetyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline with Raney nickel catalyst at high temperature and pressure gave only *trans*-2-ethyldecahydro*iso*-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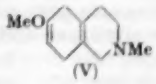
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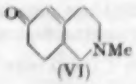
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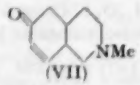
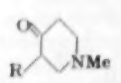
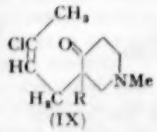
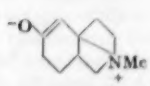

(VII)

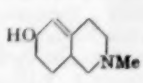
quinoline. The infrared absorption of the ketone (IV) showed a carbonyl band at 5·85 μ, characteristic of a saturated ketone, with no band at 6 μ characteristic of a conjugated carbonyl group. It is evident, therefore, that there is in this amino-ketone no interaction between the carbonyl group and the nitrogen atom, resulting in transannular amide-type neutralisation, such as is shown by cryptopine and similar keto-bases containing a many-membered heterocyclic ring.[9] Molecular models of the ketone show that the carbonyl and the methylimino-group are widely separated, so that interaction would be unlikely.

Reduction of 1 : 2 : 3 : 4-tetrahydro-6-methoxy-2-methyl*iso*quinoline (II; R = Me) with sodium and methanol in liquid ammonia gave a hexahydro*iso*quinoline, presumably (V), according to rules postulated by Birch [10] governing the mode of addition of hydrogen to anisole and its derivatives in such reductions. The product was not isolated; it gave on hydrolysis an unsaturated ketonic base, $\lambda_{max.}$ 227·5 mμ (ε 10,000). The expected structure for the base is 1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-octahydro-2-methyl-6-oxo*iso*quinoline (VI) (calc. $\lambda_{max.}$ 244 mμ), but the low value of $\lambda_{max.}$ agrees more satisfactorily with the structure (VII) (calc. $\lambda_{max.}$ 227 mμ), the calculated values being based on Woodward's rules [11] concerning the ultraviolet absorption of αβ-unsaturated carbonyl systems. Proof of structure (VI) was provided by unambiguous synthesis. Preliminary experiments showed that 3-cyano-1-methyl-4-piperidone (VIII; R = CN) and 3-methoxycarbonyl-1-methyl-4-piperidone (VIII; R = CO_2Me) condensed with 1 : 3-dichlorobut-2-ene [12] to give the chloro-ketones


(VIII)


(IX)


(X)


(XI)

(IX; R = CN) and (IX; R = CO_2Me) respectively, but these compounds could not be cyclised with sulphuric acid to *iso*quinolines. However, the ester (VIII; R = CO_2Me) with

[7] Buck, *J. Amer. Chem. Soc.*, 1934, **56**, 1769; Davies, Haworth, Jones, and Lamberton, *J.*, 1947, 191.
[8] Witkop, *J. Amer. Chem. Soc.*, 1949, **71**, 2559.
[9] Anet, Bailey, and Robinson, *Chem. and Ind.*, 1953, 944; Leonard and co-workers, *J. Amer. Chem. Soc.*, 1954, **76**, 630, 3463, 5708.
[10] Birch, *J.*, 1944, 430.
[11] Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 76.
[12] Cf. Wichterle and co-workers, *Coll. Czech. Chem. Comm.*, 1947, **12**, 101, 129; 1948, **13**, 300.

4-diethylaminobutan-2-one methiodide (Robinson–Mannich reaction [13]) gave an intermediate product which on prolonged hydrolysis yielded 1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-octahydro-2-methyl-6-oxo*iso*quinoline (VI), $\lambda_{max.}$ 227·5 mμ, identical with the previous product.

The compound (VI) was synthesised simultaneously by Georgian [14] by a closely similar method. We are grateful to Professor Georgian for advance information about his investigations in this field.

It is evident, therefore, that the unsaturated keto-base (VI) shows ultraviolet absorption at an unexpectedly short wavelength. Other examples of this abnormal behaviour are at present under investigation, but it may be suggested here that the nitrogen atom, although not directly attached to the chromophore, raises the energy associated with the electronic disturbances therein, so that maximum ultraviolet absorption occurs at a shorter wavelength. A dipolar structure such as (X) may make an important contribution to the stable state of the molecule.

The methiodide of the base (VI) also shows this abnormality ($\lambda_{max.}$ 222 mμ; ε 27,400). Here the effect is enhanced, presumably by the positive charge carried by the nitrogen atom.

Catalytic hydrogenation of the base (VI) gave the saturated ketone (IV) or the alcohol (III), according to the conditions, and Meerwein–Ponndorf reduction afforded the unsaturated alcohol (XI).

We are indebted to Dr. J. Raventós, of Imperial Chemical Industries Limited (Pharmaceuticals), for a pharmacological test on decahydro-6-hydroxy-2-methyl*iso*quinoline (III). By the method of Davies, Raventós, and Walpole [15] it was found that the compound, injected intravenously into rats, was ineffective at 20 mg./kg., but at 100 mg./kg. gave an increase in the reaction time to painful stimulus similar to that obtained with 3 mg./kg. of morphine.

Experimental

Most of the analyses are by Mr. F. C. Hall. Ultraviolet absorption measurements are in MeOH solution.

m-*Methoxyphenethylamine.*—*m*-Methoxybenzaldehyde, obtained by methylation of *m*-hydroxybenzaldehyde,[16] was condensed with nitromethane to give *m*-methoxy-ω-nitrostyrene.[17] The crystalline nitrostyrene (17 g.) in dry ether (800 c.c.) was added dropwise to a suspension of lithium aluminium hydride (12 g.) in dry ether (400 c.c.) during 1 hr., with constant shaking. After a further 2 hr. " Celite 545 " (3 g.) was added, followed by water (75 c.c.), cautiously, with shaking and ice-cooling. The ethereal solution was decanted, dried (KOH), and evaporated. The residual *m*-methoxyphenethylamine distilled at 140°/11 mm. (11·5 g.) [18] (Helfer [19] gives b. p. 122—123°/7 mm.).

1 : 2 : 3 : 4-*Tetrahydro-6-hydroxy-2-methylisoquinoline* (II; R = H).—Application of the Pictet–Spengler synthesis to the foregoing base gave 1 : 2 : 3 : 4-tetrahydro-6-methoxy*iso*quinoline,[7, 19] which on methylation with formaldehyde and formic acid [7, 19] afforded 1 : 2 : 3 : 4-tetrahydro-6-methoxy-2-methyl*iso*quinoline (II; R = Me). The latter base (2·0 g.) was heated at 180° with concentrated hydrochloric acid (18 c.c.) for 3 hr.[7] The clear solution was evaporated to dryness *in vacuo*, the crystalline residue dissolved in water (15 c.c.), and the solution brought to pH 10—10·5 with solid potassium carbonate. The precipitated phenolic base was collected and washed with a little cold water. 1 : 2 : 3 : 4-*Tetrahydro-6-hydroxy-2-methylisoquinoline* separated from water in diamond-shaped plates, m. p. 182—183° (1·7 g.) (Found : C, 73·8; H, 8·05. $C_{10}H_{13}ON$ requires C, 73·6; H, 8·0%). The hydrochloride crystallised from ether–ethanol in pale cream-coloured nodules, m. p. 234—235° (decomp.) (Buck [7] gives m. p. 236°).

Decahydro-6-hydroxy-2-methylisoquinoline (III).—The foregoing base (5 g.) in ethanol (50 c.c.) was hydrogenated at 160°/150 atm. in the presence of " W7 " Raney nickel [20] and a trace of

[13] Organic Reactions, Vol. I, p. 321.
[14] Georgian, *Chem. and Ind.*, 1954, 930.
[15] Davies, Raventós, and Walpole, *Brit. J. Pharmacol.*, 1946, **1**, 255.
[16] *Org. Synth.*, 1949, **29**, 64.
[17] Gulland and Virden, *J.*, 1929, 1791.
[18] Cf. Nystrom and Brown, *J. Amer. Chem. Soc.*, 1948 **70**, 3738; Erne and Ramirez, *Helv. Chim. Acta*, 1950, **33**, 912.
[19] Helfer, *ibid.*, 1924, **7**, 945.
[20] Adkins and Billica, *J. Amer. Chem. Soc.*, 1948, **70**, 695; *Org. Synth.*, Coll. Vol. III, p. 181.

sodium hydroxide for 12 hr. The filtered solution gave on evaporation *decahydro-6-hydroxy-2-methylisoquinoline*, b. p. 150—160° (bath)/1 mm. (4·5 g.) (Found : C, 70·8; H, 11·25; N, 8·0. $C_{10}H_{19}ON$ requires C, 71·0; H, 11·2; N, 8·3%), readily soluble in water and the usual organic solvents. Infrared absorption : strong hydroxyl band at 3·0 μ; no aromatic ring bands in the 6—7 μ region. The *methiodide* separated from ethanol in needles, m. p. 273° (Found : C, 42·2; H, 7·1. $C_{11}H_{22}ONI$ requires C, 42·2; H, 7·1%). The *α-naphthylurethane* crystallised from ethanol in plates, m. p. 74° (Found : C, 74·6; H, 7·75. $C_{21}H_{26}O_2N_2$ requires C, 74·6; H, 7·7%). The *picrate* separated from methanol in needles, m. p. 178° (Found : C, 48·4; H, 5·6. $C_{16}H_{22}O_8N_4$ requires C, 48·2; H, 5·5%).

Decahydro-2-methyl-6-oxoisoquinoline (IV).—The above hydroxy-base (4 g.) in acetic acid (12 c.c.) was treated with chromic acid (1·7 g.) in water (5 c.c.). After 6 hr. at 60—70° the solution was cooled, diluted, basified with potassium hydroxide, and extracted with ether. The extract was dried (K_2CO_3) and evaporated. The residual *decahydro-2-methyl-6-oxoisoquinoline* distilled at 120—130° (bath)/0·5 mm. (3·2 g.) (Found : C, 71·7; H, 10·2. $C_{10}H_{17}ON$ requires C, 71·9; H, 10·2%). Infrared absorption : saturated carbonyl band at 5·85 μ; no hydroxyl band in 3 μ region. The *methiodide* crystallised from ethanol in needles, m. p. 243° (Found : C, 42·9; H, 6·6. $C_{11}H_{20}ONI$ requires C, 42·7; H, 6·5%). The *picrate* separated from methanol in needles, m. p. 142° (Found : C, 48·5; H, 5·0. $C_{16}H_{20}O_8N_4$ requires C, 48·5; H, 5·1%), but in a few days was transformed into a modification of m. p. 218° (Found : C, 48·5; H, 5·3%), which on crystallisation from methanol reverted to the form, m. p. 142°.

1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-*Octahydro-2-methyl-6-oxoisoquinoline* (VI).—1 : 2 : 3 : 4-Tetrahydro-6-methoxy-2-methyl*iso*quinoline (10 g.) in methanol (50 c.c.) was added to liquid ammonia (150 c.c.), followed by sodium (12 g.), in small portions during 30 min., with vigorous stirring, the blue colour being allowed to disappear between each addition. Ether was then added cautiously, followed by water, and the organic layer was separated. The aqueous layer was extracted several times with ether, and the combined extracts were dried and evaporated. The residual oil was boiled under reflux with 10% sulphuric acid (50 c.c.) for 1 hr. under nitrogen. The cooled solution was basified with potassium hydroxide and the product isolated with ether. Evaporation gave 1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-*octahydro-2-methyl-6-oxoisoquinoline*, b. p. 150—160° (bath)/12 mm. (5·0 g.) (Found : C, 72·6; H, 9·2. $C_{10}H_{15}ON$ requires C, 72·7; H, 9·1%), as a very pale yellow oil, soluble in water and the usual solvents. Infrared absorption : αβ-unsaturated carbonyl band at 6·0 μ; no aromatic ring bands in the 6—7 μ region. The *methiodide* separated from ethanol in needles, m. p. 208° (Found : C, 43·0; H, 5·8. $C_{11}H_{18}ONI$ requires C, 43·0; H, 5·9%) (Georgian [14] gives m. p. 209—210°, $\lambda_{max.}$ 221 mμ). The *semicarbazone* crystallised from chloroform in plates, m. p. 198° (decomp.) (Found : C, 59·5; H, 8·0. $C_{11}H_{18}ON_4$ requires C, 59·5; H, 8·1%).

Catalytic Hydrogenation of 1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-*Octahydro-2-methyl-6-oxoisoquinoline*.—(*a*) The base (0·5 g.) in ethanol (10 c.c.) was shaken in hydrogen at room temperature and pressure with Adams platinum oxide. After 1½ hr. absorption had ceased (2 mols.). Evaporation of the filtered solution gave decahydro-6-hydroxy-2-methyl*iso*quinoline, b. p. 140—150° (bath)/0·5 mm. (0·5 g.), identical with the compound described previously. The methiodide had m. p. and mixed m. p. 273°.

(*b*) In a similar hydrogenation of the base (0·5 g.) in ethanol (10 c.c.) with 5% palladium–charcoal,[21] 1 mol. of hydrogen was absorbed in 3 hr. The product, worked up as before, was decahydro-2-methyl-6-oxo*iso*quinoline, b. p. 120—130° (bath)/0·5 mm., identical with the previous material. The methiodide had m. p. and mixed m. p. 243°.

1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-*Octahydro-6-hydroxy-2-methylisoquinoline* (XI).—The unsaturated keto-base (1·0 g.) was heated on the water-bath with aluminium *iso*propoxide (0·5 g.) and dry propan-2-ol (25 c.c.) so that slow distillation occurred, until no more acetone was detected in the distillate (45 min.). Propan-2-ol (10 c.c.) was added and the mixture refluxed on the water-bath for 30 min. After evaporation of the solvent 20% aqueous potassium hydroxide (20 c.c.) was added and the product isolated with ether. Evaporation of the dried extract gave 1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-*octahydro-6-hydroxy-2-methylisoquinoline*, b. p. 120—130° (bath)/0·5 mm. (0·9 g.) (Found : C, 72·0; H, 10·1. $C_{10}H_{17}ON$ requires C, 71·8; H, 10·3%). Infrared absorption : hydroxyl band at 3·0 μ; no carbonyl band in 6 μ region. On oxidation with manganese dioxide in benzene [22] it was transformed into the original unsaturated keto-base. The *picrate* separated from methanol in needles, m. p. 163° (Found : C, 48·5; H, 5·0. $C_{16}H_{20}O_8N_4$ requires C, 48·5; H, 5·1%).

[21] *Org. Synth.*, 1946, **26**, 78.
[22] Cf. Sondheimer and Rosenkranz, *Experientia*, 1953, **9**, 62.

3-(3-Chlorobut-2-enyl)-3-cyano-1-methyl-4-piperidone (IX; R = CN).—To an ice-cold solution of sodium (1·3 g.) in absolute ethanol (60 c.c.) was added 3-cyano-1-methyl-4-piperidone hydrochloride [23] (6·6 g.) in absolute ethanol (300 c.c.). 1 : 3-Dichlorobut-2-ene (5 g.) in absolute ethanol (10 c.c.) was added dropwise with shaking. The mixture was refluxed for 3 hr., then cooled, diluted, and extracted with chloroform. The dried extract was evaporated, leaving *3-(3-chlorobut-2-enyl)-3-cyano-1-methyl-4-piperidone*, b. p. 85—90° (bath)/0·5 mm. (2·6 g.) (Found: C, 58·2; H, 6·6; Cl, 15·4. $C_{11}H_{15}ON_2Cl$ requires C, 58·3; H, 6·6; Cl, 15·7%).

3-(3-Chlorobut-2-enyl)-3-methoxycarbonyl-1-methyl-4-piperidone (IX; R = CO_2Me).—A cognate experiment with 3-methoxycarbonyl-1-methyl-4-piperidone [24] (6 g.) in absolute ethanol (10 c.c.), sodium (1 g.) in absolute ethanol (50 c.c.), and 1 : 3-dichlorobut-2-ene (4·4 g.) in absolute ethanol (10 c.c.) for 5 hr. gave the *piperidone ester*, b. p. 120—125° (bath)/0·5 mm. (3·0 g.) (Found: C, 55·5; H, 7·0; N, 5·3. $C_{12}H_{18}O_2NCl$ requires C, 55·5; H, 6·9; N, 5·4%).

Robinson–Mannich Reaction with 3-Methoxycarbonyl-1-methyl-4-piperidone.—4-Diethylaminobutan-2-one [25] (7·15 g.) was converted into its methiodide as described by Cornforth and Robinson.[26] 3-Methoxycarbonyl-1-methyl-4-piperidone (8·55 g.) in dry benzene (40 c.c.) was added and the apparatus filled with nitrogen. A solution of potassium metal (3·25 g.) in absolute ethanol (50 c.c.) was added with swirling and ice-cooling during 5 min., swirling being continued for a further 30 min. The mixture was kept at 0° for 1 hr., then refluxed on the water-bath for 30 min. Excess of 2N-sulphuric acid was added, followed by water, the organic layer was separated, and the aqueous layer basified and extracted several times with ether. The combined extracts were dried and evaporated, and the residual oil (5·5 g.) was boiled for 6 hr. with 6N-hydrochloric acid (70 c.c.). The cooled solution was basified with potassium hydroxide; the product, isolated with ether, distilled at 150—160° (bath)/12 mm. (2·1 g.) (Found: C, 72·6; H, 8·9. Calc. for $C_{10}H_{15}ON$: C, 72·7; H, 9·1%). Ultraviolet absorption: max. at 227·5 mμ (ε 9500). The methiodide (Found: C, 42·8; H, 6·0. Calc. for $C_{11}H_{18}ONI$: C, 43·0; H, 5·9%) had m. p. 208—209° (decomp.), and the semicarbazone (Found: C, 59·6; H, 8·0. Calc. for $C_{11}H_{18}ON_4$: C, 59·5; H, 8·1%) had m. p. 198° (decomp.), both alone and mixed with the corresponding derivatives obtained from the reduction and hydrolysis of 1 : 2 : 3 : 4-tetrahydro-6-methoxy-2-methyl*iso*quinoline.

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Department of Chemistry, Queen's University, Belfast. [*Received, August 17th*, 1955.]

[23] Cook and Reed, *J.*, 1945, 399.
[24] Cf. Prill and McElvain, *J. Amer. Chem. Soc.*, 1933, **55**, 1233; McElvain and Rorig, *ibid.*, 1948, **70**, 1820.
[25] Wilds and Shunk, *ibid.*, 1943, **65**, 469.
[26] Cornforth and Robinson, *J.*, 1949, 1855.

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68. *Infrared Absorption of Halogeno-steroids.*

By D. H. R. Barton, J. E. Page, and C. W. Shoppee.

An examination of the infrared absorption spectra of 2-, 3-, 5-, 6-, and 7-chloro-steroids and 2-, 3-, 4-, 5-, 6-, and 7-bromo-steroids, in which the stereochemical configurations of the carbon–halogen linkages are known, has revealed that the stretching frequency for an equatorial carbon–halogen linkage is greater than that for the corresponding axial linkage.

The absorption frequencies of carbon–halogen linkages in simple alkyl halides [1] and halogeno*cyclo*hexanes [2] have received considerable attention and have been used in studies of internal rotation in these compounds. No information on the absorption of carbon–halogen linkages in halogeno-steroids has been published; Corey, Sneen, Danaher,

[1] Brown and Sheppard, *Trans. Faraday Soc.*, 1954, **50**, 1164; Mizushima, "Structure of Molecules and Internal Rotation," Academic Press, New York, 1954, and references there cited.
[2] (*a*) Larnaudie, *Compt. rend.*, 1952, **235**, 154; 1953, **236**, 909; *J. Phys. Radium*, 1954, **15**, 650; (*b*) Kozima, Sakashita, and Maeda, *J. Amer. Chem. Soc.*, 1954, **76**, 1965.

Young, and Rutledge [3] reported that an equatorial carbon–chlorine linkage absorbs at a higher frequency than an axial, but did not provide supporting evidence. We believe that infrared spectroscopy is of value for assigning the conformations of carbon–halogen linkages in halogeno-steroids and that therefore the spectra of such compounds deserve more attention.

Jones, Ramsay, Herling, and Dobriner [4] (see also Corey [5]) developed a carbonyl stretching frequency method for assigning the conformations of carbon–bromine linkages in α-bromoketo-steroids; the method is, however, limited to α-halogenoketo-steroids. A method that is dependent on the carbon–halogen stretching frequency would have a much wider application.

One of us [6] has postulated that in general the stretching frequency for an equatorial substituent in ring A of a steroid is slightly greater than that for an axial substituent. In order to extend the possible applications of such a generalisation we have examined the infrared spectra of several pairs of epimeric bromo- and chloro-steroids and have been able to show that an equatorial carbon–halogen linkage absorbs at a higher frequency than an axial. The carbon–chlorine and carbon–bromine bands are fairly strong and, since they appear in a spectral region in which alicyclic compounds do not absorb strongly, the bands can be readily identified.

Since axial carbon–bromine linkages absorb below 650 cm.$^{-1}$, it was necessary to examine the halogeno-steroids over the 1000—400 cm.$^{-1}$ region by means of a spectrophotometer fitted with a potassium bromide prism. No information on the infrared absorption of steroids at frequencies below 650 cm.$^{-1}$ has so far been published. In view of the importance of the carbon–halogen bands, it is recommended that all reference spectra of chloro- and bromo-steroids should be recorded over the 1000—400 cm.$^{-1}$ region.

Certain simple alkyl halides [1] and halogeno*cyclo*hexanes [2] exhibit internal rotation and in the solid and the liquid state yield different infrared and Raman spectra. Thus the infrared spectrum of a liquid *n*-propyl halide has two carbon–halogen stretching bands (*gauche* and *trans* forms of the molecule) and that of the solid, one band (*trans* form). The halogeno-steroids would not be expected to show internal rotation and both their carbon disulphide solutions and Nujol mulls yield similar spectra. Nevertheless, many chloro- and bromo-steroids exhibited more than one band in the carbon–halogen stretching region, the stronger band, which is listed in the Tables, usually appearing at a slightly higher frequency than the weaker band.

The observations summarised in Table 1 show that an equatorial carbon–chlorine linkage in 2- (755 cm.$^{-1}$), 3- (782—750 cm.$^{-1}$), and 7-chloro-steroids (749 cm.$^{-1}$) has a higher stretching frequency than the corresponding axial linkage (693, 730—617, and 588 cm.$^{-1}$, respectively). The absorption frequency differences for the epimeric pairs are greater than those reported for epimeric hydroxy-,[6b–d] methoxy-,[6a] acetoxy-,[6a,6f] and deutero-steroids.[3] Unexpectedly strong bands at about 1258, 1275 and 1162, 1168, and 1275 cm.$^{-1}$ in the infrared spectra of 3α-chlorocholestane (Fig. *a*; C.S. No. 301), 3α-chlorocoprostane (Fig. *b*; C.S. No. 302), 3β-chlorocholestane (Fig. *c*; C.S. No. 303), and 3β-chlorocoprostane (Fig. *d*; C.S. No. 304), respectively, are also worthy of notice; similar bands appear in the spectra of the corresponding bromo-steroids.

The carbon–chlorine stretching frequencies for the dichloro-steroids (see Table 2) appear within, or close to, the ranges observed for monochloro-steroids. In compounds containing two equatorial or two axial chlorine atoms it is not possible to assign the equatorial or axial absorption bands to specific chlorine atoms; this is indicated in the Table by the insertion of " ? " after the frequency values for those bands whose assignment is uncertain.

The characteristic absorption bands for other substituents in the steroids listed appear at

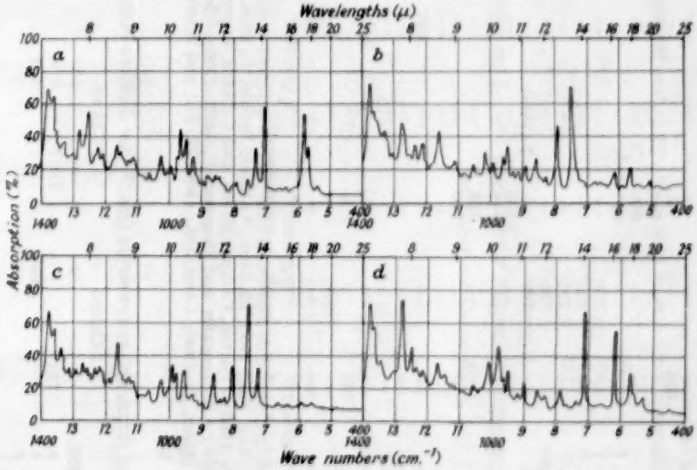
[3] Corey, Sneen, Danaher, Young, and Rutledge, *Chem. and Ind.*, 1954, 1294.
[4] Jones, Ramsay, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2828.
[5] Corey, *ibid.*, 1953, **75**, 2301, 3297.
[6] (*a*) Page, *J.*, 1955, 2017; see also (*b*) Fürst, Kuhn, Scotoni, and Günthard, *Helv. Chim. Acta*, 1952, **35**, 951; (*c*) Cole, Jones, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 5571; (*d*) Rosenkrantz and and Zablow, *ibid.*, 1953, **75**, 903; (*e*) Ref. 3; (*f*) Stoll, Petrzilka, Rutschmann, Hofmann, and Günthard, *Helv. Chim. Acta*, 1954, **37**, 2039; (*g*) Rosenkrantz and Skogstrom, *J. Amer. Chem. Soc.*, 1955, **77**, 2237.

the expected frequencies. Thus the equatorial hydroxyl group in 2α-chlorocholestan-3β-ol absorbs at about 1056 cm.$^{-1}$, and the axial hydroxyl groups in 2β-chlorocholestan-3α-ol and 3α-chlorocholestan-2β-ol absorb at 1005 and 1012 cm.$^{-1}$, respectively.

The equatorial carbon–bromine linkages (see Table 3) for 2- and 3-bromo-steroids absorb at about 754—708 and 708—704 cm.$^{-1}$, respectively, and the corresponding axial linkages at about 662 and 692—591 cm.$^{-1}$, respectively. Equatorial and axial carbon–halogen linkages in dibromo- and bromochloro-steroids (see Tables 4 and 5) absorb in the same frequency ranges (see below) as the corresponding linkages in monohalogeno-steroids. It is possible to distinguish without difficulty between equatorial and axial halogen atoms.

The observation that an equatorial carbon–halogen linkage absorbs at a higher frequency than an axial linkage may be explained qualitatively by an extension of the suggestion, advanced for 3-hydroxy-steroids by Cole, Jones, and Dobriner,[6c] that the stretching motion of an equatorial 3-substituent causes appreciable expansions and contractions of the

Infrared spectra (1400—400 *cm.*$^{-1}$) *of* (*a*) 3α-*chlorocholestane*, (*b*) 3α-*chlorocoprostane*, (*c*) 3β-*chlorocholestane*, *and* (*d*) 3β-*chlorocoprostane in* CS_2.



*cyclo*hexane ring, whereas the stretching motion of an axial 3-substituent is largely normal to the plane of the ring and will have a smaller effect; the restoring force acting on $C_{(3)}$ should therefore be less for the axial than for the equatorial motion and should induce a lower vibration frequency. This hypothesis is supported by the spectra of α-substituted bromo-steroids.

The absorption frequencies observed for particular classes of equatorial or axial carbon–chlorine or carbon–bromine bands show close agreement with each other; the number of compounds examined with only one halogen atom and without unsaturation or neighbouring α-substituents was, however, small. Many of the halides examined were 1 : 2-dihalides or related halogenohydrins; it is of interest to examine the effect of neighbouring α-substitution on the carbon–halogen band frequency. So far as available data show, substitution of α-axial chlorine has a greater influence than α-axial hydroxyl on the absorption frequency for axial chlorine. The same applies to the effect of α-axial hydroxyl and bromine on the absorption frequency for axial bromine. The effect of neighbouring α-axial bromine on the frequency for axial bromine is profound, a shift of about 150 cm.$^{-1}$ towards lower frequencies being observed. On the other hand, α-equatorial bromine has no effect on the frequency for equatorial bromine. These effects are illustrated more specifically by the following examples. Cholestanyl bromide has an equatorial carbon–bromine frequency of 706 cm.$^{-1}$, and the stereoisomeric *epi*cholestanyl bromide an axial carbon–bromine frequency of 690 cm.$^{-1}$. The diequatorial 2α : 3β-dibromocholestane has carbon–bromine frequencies at 750 and 682 cm.$^{-1}$, frequencies only slightly displaced

TABLE 1. *Carbon–chlorine stretching frequency assignments (cm.$^{-1}$) for monochloro-steroids in CS_2 solution.*

No.	Compound	Ref.	2-Chloro		3-Chloro		5-Chloro		6-Chloro		7-Chloro	
			e *	*a* *	*e*	*a*	*e*	*a*	*e*	*a*	*e*	*a*
1	2α-Chlorocholestan-3β-ol	*a*	755	—	—	—	—	—	—	—	—	—
2	2β-Chlorocholestan-3α-ol	*b*	—	693	—	—	—	—	—	—	—	—
3	3α-Chlorocholestane	*c*	—	—	—	707	—	—	—	—	—	—
4	3α-Chlorocholestan-2β-ol	*b*	—	—	—	699	—	—	—	—	—	—
5	3α-Chlorocholestan-5-ene	*d*	—	—	—	617	—	—	—	—	—	—
6	3α-Chlorocoprostane	*e*	—	—	750	—	—	—	—	—	—	—
7	3β-Chlorocholestane	*c*	—	—	755	—	—	—	—	—	—	—
8	3β-Chloro-3α-methylcholestane	*f*	—	—	782	—	—	—	—	—	—	—
9	3β-Chlorocholest-5-ene	*g*	—	—	760	—	—	—	—	—	—	—
10	3β-Chlorostigmast-5-ene	*h*	—	—	760	—	—	—	—	—	—	—
11	3β-Chlorocoprostane	*i*	—	—	—	709	—	—	—	—	—	—
12	3β-Chlorocoprostan-6-one	*j*	—	—	—	711	—	—	—	—	—	—
13	3β-Chlorocoprostan-6β-ol	*j*	—	—	—	726	—	—	—	—	—	—
14	3β-Chlorocoprostan-6β-yl acetate	*j*	—	—	—	730	—	—	—	—	—	—
15	5α-Chloro-6β-hydroxycholestan-3β-yl benzoate	*k*	—	—	—	—	—	685	—	—	—	—
16	6β-Chlorocholestane-3β : 5α-diol	*l*	—	—	—	—	—	—	—	706	—	—
17	6β-Chloro-5α-hydroxycholestan-3β-yl acetate	*k*	—	—	—	—	—	—	—	706	—	—
18	6β-Chloro-5α-hydroxycholestan-3β-yl benzoate	*k*	—	—	—	—	—	—	—	707	—	—
19	7α-Chlorocholestane	*m*	—	—	—	—	—	—	—	—	—	588
20	7β-Chlorocholestane	*m*	—	—	—	—	—	—	—	—	749	—

* *a* = axial; *e* = equatorial.

[a] Beereboom, Djerassi, Ginsburg, and Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 3500; [b] Alt and Barton, *J.*, 1954, 4284; [c] Shoppee, *J.*, 1946, 1138; [d] Shoppee and Summers, *J.*, 1952, 1790; [e] Lewis and Shoppee, *J.*, 1955, 1365; [f] Barton, Campos-Neves, and Cookson, unpublished work; [g] Diels and Blumberg, *Ber.*, 1911, **44**, 2847; [h] Windaus and Hauth, *Ber.*, 1906, **39**, 4378; [i] Bridgewater and Shoppee, *J.*, 1953, 1709; [j] Jones, Shoppee, and Summers, unpublished work; [k] Spring and Swain, *J.*, 1939, 1356; [l] Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 370, and references there cited; [m] Cremlyn and Shoppee, *J.*, 1954, 3794.

TABLE 2. *Carbon–chlorine stretching frequency assignments (cm.$^{-1}$) for dichloro-steroids in CS_2 solution.*

No.	Compound	Ref.	2-Chloro		3-Chloro		5-Chloro		6-Chloro	
			e	*a*	*e*	*a*	*e*	*a*	*e*	*a*
21	2α : 3β-Dichlorocholestane	*b*	784?	—	738?	—	—	—	—	—
22	2β : 3α-Dichlorocholestane	*b*	—	639	—	639	—	—	—	—
23	5α : 6α-Dichlorocholestan-3β-ol	*l*	—	—	—	—	—	684	777	—
24	5α : 6β-Dichlorocholestane	*l*	—	—	—	—	—	652	—	652
25	5α : 6β-Dichlorocholestan-3β-ol	*l*	—	—	—	—	—	650	—	650
26	5α : 6β-Dichlorocholestan-3β-yl acetate	*l*	—	—	—	—	—	648	—	648
27	5α : 6β-Dichlorocholestan-3β-yl benzoate	*l*	—	—	—	—	—	652	—	652

TABLE 3. *Carbon–bromine stretching frequency assignments (cm.$^{-1}$) for monobromo-steroids in CS_2 solution.*

No.	Compound	Ref.	2-Bromo		3-Bromo		5-Bromo		7-Bromo	
			e	*a*	*e*	*a*	*e*	*a*	*e*	*a*
28	2α-Bromocholestan-3α-ol	*n*	754	—	—	—	—	—	—	—
29	2α-Bromocholestan-3β-ol	*n*	708	—	—	—	—	—	—	—
30	2β-Bromocholestan-3α-ol	*b*	—	662	—	—	—	—	—	—
31	3α-Bromocholestane	*o*	—	—	—	690	—	—	—	—
32	3α-Bromocholest-5-ene	*d*	—	—	—	591	—	—	—	—
33	3α-Bromocoprostane	*e*	—	—	708	—	—	—	—	—
34	3β-Bromocholestane	*o*	—	—	706	—	—	—	—	—
35	3β-Bromocholest-5-ene	*o*	—	—	704	—	—	—	—	—
36	3β-Bromocoprostane	*i*	—	—	—	692	—	—	—	—
37	5α-Bromo-6β-hydroxycholestan-3β-yl benzoate	*p*	—	—	—	—	—	668	—	—
38	7β-Bromocholestane	*m*	—	—	—	—	—	—	710	—

[a] Fieser and Huang, *J. Amer. Chem. Soc.*, 1953, **75**, 4837; Corey, *ibid.*, p. 4832; [b] Roberts, Shoppee, and Stephenson, *J.*, 1954, 2705; [c] Barton, Miller, and Young, *J.*, 1951, 2598.

TABLE 4. *Carbon–bromine stretching frequency assignments (cm.$^{-1}$) for dibromo-steroids in CS_2 solution.*

No.	Compound	Ref.	2-Bromo		3-Bromo		4-Bromo		5-Bromo		6-Bromo	
			e	*a*	*e*	*a*	*e*	*a*	*e*	*a*	*e*	*a*
39	2α : 3β-Dibromocholestane	*b*	750?	—	682?	—	—	—	—	—	—	—
40	2β : 3α-Dibromocholestane	*b*	—	548	—	542	—	—	—	—	—	—
41	3α : 4β-Dibromocholestane	*b*	—	—	—	566?	—	547?	—	—	—	—
42	3β : 4α-Dibromocholestane	*b*	—	—	716?	—	693?	—	—	—	—	—
43	5α : 6β-Dibromocholestan-3β-yl benzoate	*q*	—	—	—	—	—	—	—	618?	—	566?
44	5β : 6α-Dibromocholestane	*q*	—	—	—	—	—	—	746?	—	707?	—
45	5β : 6α-Dibromocholestan-3β-yl benzoate	*q*	—	—	—	—	—	—	747?	—	722?	—

[a] Ref. 7 and references there cited.

TABLE 5. *Carbon–chlorine and carbon–bromine stretching frequency assignments (cm.$^{-1}$) for chlorobromo-steroids in CS_2 solution.*

No.	Compound	Ref.	2-Chloro		3-Chloro		2-Bromo		3-Bromo	
			e	*a*	*e*	*a*	*e*	*a*	*e*	*a*
46	3β-Bromo-2α-chlorocholestane	*b*	772	—	—	—	—	—	700	—
47	3α-Bromo-2β-chlorocholestane	*b*	—	601	—	—	—	—	—	601
48	2β-Bromo-3α-chlorocholestane	*b*	—	—	—	587	—	587	—	—
49	2α-Bromo-3β-chlorocholestane	*b*	—	—	772	—	703	—	—	—

TABLE 6. *Carbon–bromine stretching frequency assignments (cm.$^{-1}$) for 23-bromo-isosapogenins in CS_2 solution.*

No.	Compound	Ref.	*e*	*a*
50	23a-Bromo-12-oxo-5α : 22a-spirost-9(11)-en-3β-yl acetate	*r*	727	—
51	23b-Bromo-12-oxo-5α : 22a-spirost-9(11)-en-3β-yl acetate	*r*	—	655
52	11α : 23a-Dibromo-12-oxo-5α : 22a-spirostan-3β-yl acetate	*r*	728	—
53	11α : 23b-Dibromo-12-oxo-5α : 22a-spirostan-3β-yl acetate	*r*	—	652

[a] Ref. 10.

relative to that for cholestanyl bromide. In contrast the diaxial 2β : 3α-dibromocholestane shows carbon–bromine frequencies at 548 and 542 cm.$^{-1}$, frequencies greatly displaced relative to that for *epi*cholestanyl bromide. The simplest explanation for the difference in behaviour between 2α : 3β- and 2β : 3α-dibromocholestane is the importance of the weight of the neighbouring substituent and its coplanarity with the carbon–bromine and α-carbon atoms. As is well known,[7] diaxially substituted *cyclo*hexanes satisfy this requirement, whereas their diequatorial analogues do not.

The absorption frequencies of equatorial and axial carbon–chlorine linkages in the monohalogeno-steroids examined are respectively 56—39 and 37—17 cm.$^{-1}$ higher than those for the corresponding carbon–bromine linkages. The frequencies for the equatorial linkages in 3β-chloro-, 3β-bromo-, and 3β-iodo-cholest-5-ene (the only simple iodo-steroid available) [8] are 760, 704, and 672 cm.$^{-1}$, respectively. These values are close to those reported for monohalogeno*cyclo*hexanes by Larnaudie [2a] (equatorial and axial chlorine, 742 and 688 cm.$^{-1}$, respectively; equatorial and axial bromine, 685 and 658 cm.$^{-1}$, respectively; equatorial and axial iodine, 654 and 639 cm.$^{-1}$, respectively), but the values for bromine and iodine linkages are considerably higher than those quoted for simpler compounds by Bellamy [9] (600—500 cm.$^{-1}$ and near 500 cm.$^{-1}$, respectively).

In monohalogeno-steroids, the apparent molecular extinction coefficient of an equatorial carbon–halogen absorption band (carbon–chlorine, 150—100; carbon–bromine, 135—70) was usually greater than that of the corresponding axial absorption band (carbon–chlorine, 110—70; carbon–bromine, 95—45); the axial bands sometimes split into several relatively weak components. The apparent molecular extinction coefficients for the carbon–halogen stretching bands listed in Tables 1 and 3 for 3α-chloro-, 3β-chloro-, 3α-bromo-, and 3β-bromo-cholestane were about 75, 150, 55, and 135, respectively.

Dickson and Page [10] originally believed that the absorption band at about 726 cm.$^{-1}$ in the absorption spectrum of a 23a-bromo-*iso*sapogenin [11] was associated with a carbon–bromine linkage, but they discounted the suggestion because of the lack of supporting infrared evidence. A re-examination of the spectra of 23a-bromo- and 23b-bromo-*iso*sapogenins [11] over the 1000—400 cm.$^{-1}$ region (see Table 6) has revealed strong absorption bands at about 727 and 654 cm.$^{-1}$, respectively, suggesting in the light of the observations reported above that, provided the bromine atom in bromo*iso*sapogenins is actually at $C_{(23)}$, the carbon–bromine linkages at $C_{(23)}$ are equatorial and axial, respectively.

Experimental

The halogeno-steroids were examined over the 4000—650 cm.$^{-1}$ and 1000—400 cm.$^{-1}$ spectral regions by means of a Perkin-Elmer Corporation, Model 21, double-beam, infrared spectrophotometer fitted with a sodium chloride or potassium bromide prism, respectively. Measurements with the sodium chloride prism were made as described by Dickson, Page, and Rogers.[12]

For potassium bromide prism measurements the instrument was calibrated by reference to known bands in the absorption spectra of ammonia gas and of the atmosphere; [13] the accuracy of frequency measurements for sharp absorption bands was probably greater than ±2 cm.$^{-1}$ over the range 1000—400 cm.$^{-1}$. The halogeno-steroids were examined as 1·0% (w/v) carbon disulphide solutions in a 2·0 mm. potassium bromide cell; compensation for solvent absorption was achieved by passing the reference beam of the spectrophotometer through pure carbon disulphide in a matched cell. Carbon disulphide absorbs weakly at about 652 cm.$^{-1}$ and strongly at about 422 cm.$^{-1}$.

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[7] Barton and Miller, *ibid.*, 1950, **72**, 1066.
[8] Beynon, Heilbron, and Spring, *J.*, 1936, 907.
[9] Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 269.
[10] Dickson and Page, *J.*, 1955, 447.
[11] Mueller and Norton, *J. Amer. Chem. Soc.*, 1954, **76**, 749.
[12] Dickson, Page, and Rogers, *J.*, 1955, 443.
[13] Roberts, *J. Sci. Instr.*, 1954, **31**, 226, and references there cited.

69. *New Trypanocides. Part I. Quaternary Salts derived from 2 : 7-Diaminophenanthridine and the Attempted Preparation of Quaternary Salts from 2 : 7-Diamino-9-anilinophenanthridine.*

By M. Davis.

2 : 7-Diamino- and 2 : 7-di(ethoxycarbonylamino)-10-methylphenanthridinium salts have been prepared by two routes. 2 : 7-Diamino-9-anilino- and -9-*p*-aminoanilino-phenanthridine have been prepared from 9-chloro-2 : 7-dinitrophenanthridine. Attempts to convert the last two bases into quaternary derivatives analogous to Dimidium and Trimidium salts were unsuccessful.

Although the trypanocidal activity of many 9-substituted phenanthridinium salts has been studied in detail, the examination of similar compounds containing a 9-anilino-group or without a 9-substituent has until recently been neglected. The synthesis of 2 : 7-diamino- (IX; R = H) and 2 : 7-di(ethoxycarbonylamino)-10-methylphenanthridinium salts (IX; R = CO_2Et) was therefore undertaken, and the intermediates made available in this work were employed in attempts to obtain 9-anilino- and 9-*p*-aminoanilino-derivatives (XIII; R = H and NH_2) analogous to the well known 9-phenyl- (Dimidium) and 9-*p*-aminophenyl- (Trimidium) compounds (XIV; R = H and NH_2). When this work was almost finished, a communication by Caldwell and Walls [1] described 2-, 3-, 5-, and 7-amino-10-methylphenanthridinium salts; all of these except the 5-amino-isomer had but slight trypanocidal activity.

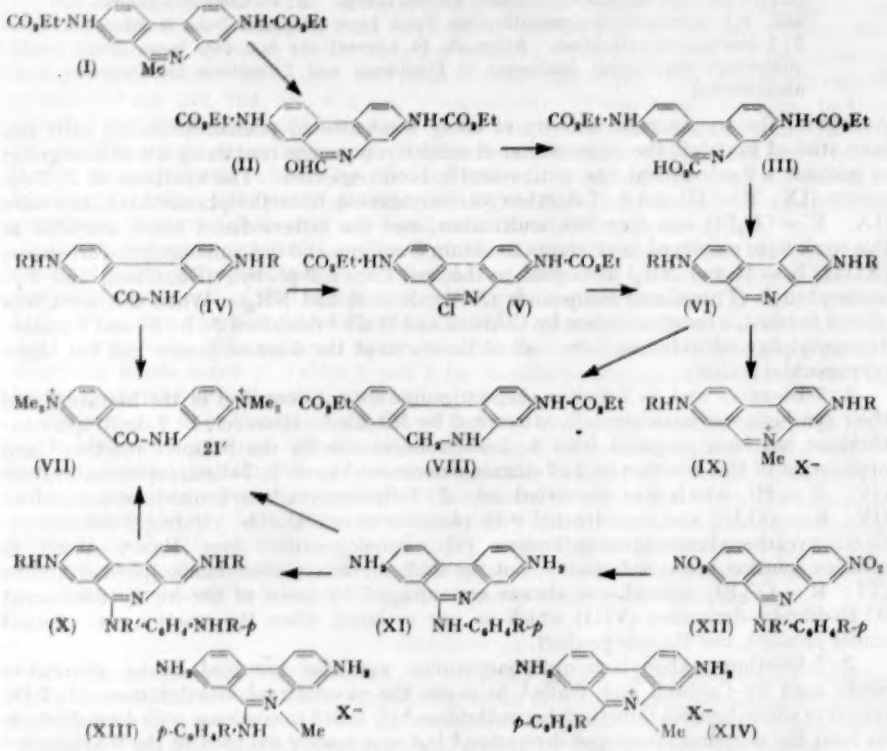
2 : 7-Diamino- and 2 : 7-dinitro-phenanthridine are not described in the literature and their synthesis was unsuccessfully attempted by Ritchie.[2] However, 2 : 7-dinitrophenanthridone has been prepared from 2 : 7-dinitrofluorenone by the Schmidt reaction [3] and application of this reaction to 2 : 7-diaminofluorenone [4] gave 2 : 7-diaminophenanthridone (IV; R = H), which was converted into 2 : 7-di(ethoxycarbonylamino)phenanthridone (IV; R = CO_2Et) and then treated with phosphorus oxychloride, yielding 9-chloro-2 : 7-di(ethoxycarbonylamino)phenanthridine (V). Dehalogenation over Raney nickel in alkaline solution proceeded readily, but the 2 : 7-di(ethoxycarbonylamino)phenanthridine (VI; R = CO_2Et) formed was always accompanied by some of the highly fluorescent 9 : 10-dihydro-derivative (VIII) which on one occasion, when the reaction was effected under pressure, was the sole product.

2 : 7-Di(ethoxycarbonylamino)phenanthridine was also prepared by an alternative route used by Caldwell and Walls [1] to make the mononitrophenanthridines. 2 : 7-Di-(ethoxycarbonylamino)-9-methylphenanthridine [5] (I) failed to condense with formaldehyde to form the dihydroxy*iso*propyl derivative,[6] but was readily oxidised to the 9-aldehyde [7] (II) by selenium dioxide in dioxan. Further oxidation with potassium permanganate in aqueous pyridine furnished the 9-carboxylic acid (III), which was decarboxylated in boiling nitrobenzene. Hydrolysis with aqueous sulphuric acid then yielded 2 : 7-diaminophenanthridine (VI; R = H).

Attempts to dehalogenate 9-chloro-2 : 7-dinitrophenanthridine [8] proved unsuccessful. Catalytic reduction over Raney nickel in alkaline solution resulted in an intractable mixture. On one occasion after reduction over platinum oxide in dioxan a small amount of what appeared to be 2 : 7-diamino-9-chlorophenanthridine or its 9 : 10-dihydro-derivative was isolated. 9-Chloro-2 : 7-dinitrophenanthridine failed to react with toluene-*p*-sulphonhydrazide in boiling chloroform or toluene [8] and was hydrolysed to 2 : 7-dinitrophenanthridone when heated with cuprous oxide–acetic anhydride in pyridine.[9]

[1] Caldwell and Walls, *J.*, 1952, 2156.
[2] Ritchie, *J. Proc. Roy. Soc. New South Wales*, 1945, **78**, 177.
[3] Walls, *J.*, 1935, 1407.
[4] Schmidt, Retzlaff, and Haid, *Annalen*, 1912, 390, 224; Barker and Barker, *J.*, 1954, 870.
[5] Walls, *J.*, 1947, 71.
[6] *Idem*, *J.*, 1934, 107.
[7] Caldwell, *J.*, 1952, 2039.
[8] Albert, Brown, and Duewell, *J.*, 1948, 1292.
[9] Edwards and Stewart, *Chem. and Ind.*, 1952, 472.

2 : 7-Di(ethoxycarbonylamino)phenanthridine formed a sparingly soluble methiodide (IX; R = CO_2Et, X^- = I^-). The more soluble metho(methyl sulphate) (IX; R = CO_2Et, X^- = $MeSO_4^-$) was obtained by brief treatment with methyl sulphate in nitrobenzene at 150°; at higher temperatures considerable decomposition occurred. Hydrolysis of the urethane groups was effected in aqueous sulphuric acid at 140°, the diamine being isolated most readily as the sparingly soluble iodide (IX; R = H, X^- = I^-). For biological testing it was converted into the more soluble chloride.



With the exception of 9-picrylaminophenanthridine,[10] no 9-anilinophenanthridine appears to have been described, although 9-amino-, 9-alkylamino-, and 9-dialkylaminophenanthridines are well known.[11] By virtue of its amidine-like structure, 9-anilinophenanthridine can theoretically exist in two tautomeric forms. Recent evidence [12] suggests that *N*-heteroaromatic amines of this type normally exist in the " amino "-form (as XI) and this structure is assumed throughout the present paper.

9-Chloro-2 : 7-dinitrophenanthridine condensed readily with *p*-nitroaniline to form the weakly basic 2 : 7-dinitro-9-*p*-nitroanilinophenanthridine (XII; R = NO_2, R' = H) which yielded an acetyl derivative (XII; R = NO_2, R' = Ac) only on prolonged boiling with acetic anhydride and pyridine. Neither the trinitro-base nor its acetyl derivative could be made to form a quaternary salt with methyl iodide, methyl sulphate, or methyl toluene-*p*-sulphonate. Morgan and Walls [13] were unable to quaternise the acetyl derivative of 9-aminophenanthridine, which observation led them to suggest that it was in fact the

[10] Morgan and Stewart, *J.*, 1938, 1304.
[11] Walls, *J.*, 1938, 389; cf. Finkelstein and Linder, *J. Amer. Chem. Soc.*, 1951, **73**, 302.
[12] Angyal and Angyal, *J.*, 1952, 1461; Angyal and Werner, *ibid.*, p. 2911; Goulden, *ibid.*, p. 2939; Short, *ibid.*, p. 4584.
[13] Morgan and Walls, *J.*, 1932, 2227.

acetyl derivative of the tautomeric imino-form. Failure to quaternise 2 : 7-dinitro-9-*p*-nitrophenylphenanthridine has also been recorded.[14]

Reduction of the derivative (XII; R = NO_2, R′ = H) with stannous chloride yielded 2 : 7-diamino-9-*p*-aminoanilinophenanthridine (XI; R = NH_2) which formed both a triacetyl (X; R = Ac, R′ = H) and a tetra-acetyl derivative (X; R = Ac, R′ = Ac). The tetra-acetyl derivative failed to react with methyl iodide in boiling methanol, but with the same reagents at 110° in a sealed tube degradation unexpectedly occurred to 2 : 7-bis-dimethylaminophenanthridone bismethiodide (VII). The same salt was obtained under similar conditions from both the triacetyl derivative (X; R = Ac, R′ = H) and the free base (XI; R = NH_2). For comparison, an authentic specimen of the bismethiodide (VII) was prepared from 2 : 7-diaminophenanthridone and identity was confirmed by examination of the ultraviolet absorption spectra. It is unlikely that degradation was preceded by formation of an unstable 10-methiodide since subsequent decomposition should then have led to the corresponding 10-methylphenanthridone. Thus Morgan and Walls [15] found that 9-dimethylaminophenanthridine 10-methiodide was decomposed by hot water into 10-methylphenanthridone.

Parallel experiments were carried out with 2 : 7-diamino-9-anilinophenanthridine (XI; R = H), prepared from 9-chloro-2 : 7-dinitrophenanthridine by condensation with aniline followed by reduction with stannous chloride. When its triacetyl derivative was heated with methyl iodide–methanol at 110°, the salt (VII) was again formed, but under milder conditions a crystalline iodide was obtained which apparently contained 0·8 *N*-methyl group. Hydrolysis of the acetyl groups, however, resulted in the recovery of the original 2 : 7-diamino-9-anilinophenanthridine.

To prevent the hydrolysis of the acetamido-groups which occurred in the degradation with methyl iodide, the amino-groups of the base (XI; R = NH_2) were protected by conversion into the urethanes. When 2 : 7-di(ethoxycarbonylamino)-9-*p*-ethoxycarbonylaminoanilinophenanthridine (X; R = CO_2Et, R′ = H) was boiled with methyl iodide in ethanol, a crystalline salt was obtained which appeared to be the hydriodide of the methylated compound (X; R = CO_2Et, R′ = Me). It was converted into the free base, which was treated further with methyl iodide at 110°, but the product was a mixture, the *N*-methyl content of which had not increased. Experiments with other alkylating agents were equally unsatisfactory.

An alternative approach to the required quaternary salts was then considered, involving the preliminary quaternisation of 9-chloro-2 : 7-dinitro- or 9-chloro-2 : 7-di(ethoxycarbonylamino)-phenanthridine and subsequent condensation with aniline or *p*-nitroaniline. In the quinoline series it is known that the reactivity of a halogen in the 2- or the 4-position is increased by quaternisation, which takes place under mild conditions.[16,17] Thus 2-iodo- and 4-chloro-quinoline methiodide readily form the 2- and the 4-anilino-derivative, respectively.[16,18] 9-Chloro-2 : 7-dinitrophenanthridine, on the other hand, was unaffected by methyl sulphate or methyl iodide in boiling benzene or toluene, and even by fusion with methyl toluene-*p*-sulphonate. Heating with methyl iodide in methanol caused hydrolysis to 2 : 7-dinitrophenanthridone. When 9-chloro-2 : 7-di(ethoxycarbonylamino)phenanthridine was heated with dry methyl iodide at 110°, the 9-chloro-group was replaced by iodine, but without concomitant quaternisation.

In a final attempt to obtain a quaternary salt, the 9-chloro-compounds were heated with tertiary bases, Morgan and Walls [15] having shown that 9-chlorophenanthridine itself condensed with trimethylamine to form trimethylphenanthrid-9-ylammonium iodide. 9-Chloro-2 : 7-di(ethoxycarbonylamino)phenanthridine was unaffected by alcoholic trimethylamine at 130—140° and gave no quaternary salt with boiling dimethylaniline, while 9-chloro-2 : 7-dinitrophenanthridine crystallised unchanged from boiling dimethylaniline.

[14] Walls and Whittaker, *J.*, 1950, 42.
[15] Morgan and Walls, *J.*, 1938, 396.
[16] Alekseeva, *J. Gen. Chem.* (*U.S.S.R.*), 1940, **10**, 263.
[17] Bergstrom, *Chem. Rev.*, 1944, **35**, 199, 211; Bahner, Easley, Pickens, Lyons, Norton, Walden, and Biggerstaff, *J. Amer. Chem. Soc.*, 1951, **73**, 3499.
[18] Brydowna, *Roczniki Chem.*, 1932, **12**, 89.

The author thanks Mrs. R. Stone for the following biological results: 2:7-Diamino-10-methylphenanthridinium chloride (IX; R = H, X^- = Cl^-) was inactive against *T. rhodesiense* and was effective, but not curative, against *T. congolense*. 2:7-Di(ethoxycarbonylamino)-10-methylphenanthridinium methyl sulphate (IX; R = CO_2Et, X^- = $MeSO_4^-$), 2:7-di(ethoxycarbonylamino)-9-*p*-ethoxycarbonylaminoanilinophenanthridine monohydrochloride, 2:7-diamino-9-anilinophenanthridine hydrochloride, and 2:7-diamino-9-*p*-aminoanilinophenanthridine hydrochloride were inactive against both organisms.

Experimental

2:7-Diaminophenanthridone.—A solution of 2:7-diaminofluorenone (31·3 g.) in concentrated sulphuric acid (250 ml.) was mechanically stirred and cooled to −30°. Sodium azide (21·8 g.) in water (75 ml.) was slowly added during 1·25 hr., at <0°, and water (75 ml.) was then added during the next 0·75 hr. The solution was poured on ice and aqueous ammonia (*d* 0·88), and the product was filtered off. Crystallisation from nitrobenzene gave 2:7-*diaminophenanthridone* (26 g., 78%) in thin prisms, m. p. 310—312° (decomp.) (Found: C, 69·0; H, 5·3; N, 18·3. $C_{13}H_{11}ON_3$ requires C, 69·3; H, 5·0; N, 18·65%). Heating the base (1 g.) with methyl iodide in methanol at 115° for 24 hr. afforded 2:7-*bisdimethylaminophenanthridone bismethiodide dihydrate* (2·6 g., 98%), yellow needles (from water), m. p. 330—334° (decomp.), which gave successively the monohydrate and the anhydrous salt when dried at 110°; the latter rapidly re-formed the dihydrate in air [Found (after drying at 100°): C, 38·9; H, 5·0; N, 7·0; I, 40·85; H_2O, 3·8; regain in air of anhydrous salt, 5·9. $C_{19}H_{25}ON_3I_2,H_2O$ requires C, 39·1; H, 4·7; N, 7·2; I, 43·5; H_2O, 3·1. $C_{19}H_{25}ON_3I_2,2H_2O$ requires H_2O, 6·0%] [$\lambda_{max.}$ in 0·1N-HCl at 336 (ε 8200), 325 (ε 9700), and 260 mμ (ε 23,300); inflexion at 269 mμ (ε 14,200)].

2:7-*Di(ethoxycarbonylamino)phenanthridone.*—2:7-Diaminophenanthridone (24·3 g.), ethyl chloroformate (25·8 ml.), and diethylaniline (43 ml.) were boiled in dry ethanol (700 ml.) for 3 hr. The cooled mixture was filtered, giving 2:7-*di(ethoxycarbonylamino)phenanthridone* which formed prisms, m. p. >360°, from dioxan (Found: C, 61·5; H, 5·4; N, 11·4. $C_{19}H_{19}O_5N_3$ requires C, 61·7; H, 5·2; N, 11·4%). The uncrystallised material (33·6 g., 84%) was pure enough for conversion into the chloro-compound.

9-*Chloro*-2:7-*di(ethoxycarbonylamino)phenanthridine.*—2:7-Di(ethoxycarbonylamino)phenanthridone (11·2 g.) was boiled with phosphorus oxychloride (55 ml.) for 30 min., and the mixture was then slowly poured into excess of aqueous ammonia and ice. The product was filtered off, washed with water, and added to boiling 2-ethoxyethanol, and the resulting solution was immediately diluted with water until cloudy; this gave 9-*chloro*-2:7-*di(ethoxycarbonylamino)phenanthridine* [7·95 g. (67%), m. p. 250—252° (decomp.)], which separated in needles, m. p. 252—254° (decomp.), from a large volume of ethanol (Found: Cl, 8·85. $C_{19}H_{18}O_4N_3Cl$ requires Cl, 9·15%).

2:7-*Di(ethoxycarbonylamino)*-9-*formylphenanthridine.*—2:7-Di(ethoxycarbonylamino)-9-methylphenanthridine (10 g.) and selenium dioxide (3·05 g.) in dioxan (400 ml.) and water (10 ml.) were boiled under reflux for 7 hr. and the solution was then filtered through alumina, which was washed with hot dioxan. The combined dioxan solutions when concentrated gave the aldehyde (7·45 g., 71%), m. p. 250—262° (decomp.), pure enough for further oxidation. For the pure aldehyde Caldwell [7] gave m. p. 270—275° (decomp.).

2:7-*Di(ethoxycarbonylamino)phenanthridine*-9-*carboxylic Acid.*—The foregoing aldehyde (12 g.) in pyridine (157 ml.) was heated to 50—55° and mechanically stirred whilst potassium permanganate (3·7 g.) in water (74·2 ml.) was added during 1·5 hr. After a further 1·5 hr. at 50—55°, the mixture was boiled and filtered, and the black residue was extracted successively with hot pyridine (2 × 150 ml.) and aqueous potassium carbonate (3 × 150 ml.). The pyridine extracts were combined with the original filtrate and concentrated under reduced pressure to 150 ml.; the carbonate extract was then added and the mixture was boiled and filtered. The residue after further extraction with potassium carbonate solution was unchanged aldehyde (2·85 g.). The combined solutions were added to acetic acid containing a small amount of dilute hydrochloric acid. The orange-red acid which separated was filtered off, washed with water, and purified by dissolution in hot N-aqueous ammonia, filtration (the insoluble residue contained more unchanged aldehyde), and addition of the filtrate to acetic acid. The reprecipitated *acid* (5·3 g., 56% allowing for recovered aldehyde) was washed with water and dried at 100° (Found: C, 60·0; H, 5·1; N, 10·6. $C_{20}H_{18}O_6N_3$ requires C, 60·45; H, 4·8; N, 10·6%).

2:7-*Di(ethoxycarbonylamino)phenanthridine.*—(*a*) The foregoing acid (5 g.) in nitrobenzene (25 ml.) was boiled for 2 min. and the solution was then cooled, mixed with ether, and filtered.

The solid was crystallised from aqueous pyridine, giving 2 : 7-*di(ethoxycarbonylamino)phenanthridine* [3·2 g. (72%), m. p. 250—253° (decomp.)] which formed blades, m. p. 252—254° (decomp.), from alcohol (Found: C, 64·3; H, 6·05; N, 11·9. $C_{19}H_{19}O_4N_3$ requires C, 64·6; H, 5·4; N, 11·9%. (*b*) A suspension of 9-chloro-2 : 7-di(ethoxycarbonylamino)phenanthridine (4 g.) in hot alcohol (400 ml.) containing potassium hydroxide (1 g.) and Raney nickel was shaken with hydrogen. When the uptake slackened fresh catalyst was added and the suspension was reheated. When the mixture began to fluoresce (owing to formation of the 9 : 10-dihydro-compound), it was heated and filtered and the solid was extracted with hot pyridine (2 × 75 ml.). The filtrate and the extracts were combined and concentrated; the residue was diluted with water and filtered. The product was crystallised from nitrobenzene and from aqueous pyridine, giving 2 : 7-di(ethoxycarbonylamino)phenanthridine (2·1 g., 58%), m. p. 253—256° (decomp.) (Found: C, 64·9; H, 5·9; N, 11·6%). On one occasion, when the chloro-compound (4 g.) was similarly reduced under pressure, the product (2·85 g.; m. p. 190—192°) was 2 : 7-*di(ethoxycarbonylamino)*-9 : 10-*dihydrophenanthridine*, m. p. 192—194° (after recrystallisation from aqueous alcohol) (Found: C, 64·2; H, 5·9; N, 11·6. $C_{19}H_{21}O_4N_3$ requires C, 64·2; H, 6·0; N, 11·8%). Its solutions are colourless with an intense violet fluorescence. The *acetyl derivative* (Found: C, 63·6; H, 6·1; N, 10·7. $C_{21}H_{23}O_5N_3$ requires C, 63·5; H, 5·8; N, 10·6%) formed feathery needles, m. p. 230—232°, from alcohol, and showed no fluorescence in solution.

2 : 7-*Diaminophenanthridine*.—2 : 7-Di(ethoxycarbonylamino)phenanthridine (0·5 g.) in concentrated sulphuric acid (1·2 ml.) and water (1 ml.) was heated at 160° for 30 min. The solution was basified and the base was filtered off, and recrystallised from water, giving 2 : 7-*diaminophenanthridine*, yellow needles, m. p. 208—210° (decomp.) (Found: C, 74·5; H, 5·3. $C_{13}H_{11}N_3$ requires C, 74·6; H, 5·3%).

2 : 7-*Di(ethoxycarbonylamino)*-10-*methylphenanthridinium Methyl Sulphate*.—2 : 7-Di(ethoxycarbonylamino)phenanthridine (3·2 g.) in redistilled nitrobenzene (50 ml.) was maintained at 150° whilst redistilled methyl sulphate (3·2 ml.) was added. After 1 min. the mixture was cooled, diluted with ether, and filtered, and the product was washed with ether. The *metho(methyl sulphate)* (4·15 g., 92%) formed orange needles, decomp. >280°, from alcohol (green fluorescent solution) (Found: N, 8·8. $C_{21}H_{23}O_6N_3S$ requires N, 8·8%). Treatment of an aqueous solution of the salt with potassium iodide afforded the corresponding *methiodide* (also obtained directly from the original base with methyl iodide–methanol), which crystallised from alcohol (green fluorescent solution) in yellow needles, decomp. >260° (Found: I, 25·4. $C_{20}H_{22}O_4N_3I$ requires I, 25·6%).

2 : 7-*Diamino*-10-*methylphenanthridinium Iodide*.—The foregoing metho(methyl sulphate) (4·15 g.) in concentrated sulphuric acid (20 ml.) and water (15 ml.) was heated at 140° for 45 min. The solution was poured into water, neutralised to pH 7 with aqueous ammonia, and filtered hot, and the filtrate was treated with solid potassium iodide and cooled. The quaternary iodide (2·75 g., 90%) was filtered off, washed with cold water and alcohol, and dried at 100°. The same *iodide* was similarly prepared from 2 : 7-di(ethoxycarbonylamino)-10-methylphenanthridinium iodide, and formed red needles, m. p. 288—290° (decomp.) (Found: N, 11·8; I, 35·7. $C_{14}H_{14}N_3I$ requires N, 11·95; I, 36·15%), from water. Boiling its aqueous solution with freshly prepared silver chloride afforded the corresponding *chloride* (Found: N, 14·5; Cl, 12·2; loss of wt. at 100°/15 mm., 9·4; regain in air, 9·3. $C_{14}H_{14}N_3Cl,1{\cdot}5H_2O$ requires N, 14·7; Cl, 12·4; H_2O, 9·4%) which formed red prisms, m. p. 278—280° (decomp.), from alcohol.

9-*Anilino*-2 : 7-*dinitrophenanthridine*.—9-Chloro-2 : 7-dinitrophenanthridine (2 g.) and aniline (9 ml.) were boiled under reflux for 1 hr.; the mixture was then cooled and diluted with ether. The product was filtered off, washed with ether, extracted with boiling water, and crystallised from acetone, giving 9-*anilino*-2 : 7-*dinitrophenanthridine* (2·2 g., 93%) in orange prisms or needles, m. p. 316—318° (Found: C, 63·4; H, 3·4; N, 15·5. $C_{19}H_{12}O_4N_4$ requires C, 63·3; H, 3·3; N, 15·55%).

2 : 7-*Dinitro*-9-p-*nitroanilinophenanthridine*, similarly prepared at 180—200° in 93% yield, formed orange needles, decomp. 350—360° (Found: C, 56·6; H, 3·0; N, 17·0. $C_{19}H_{11}O_6N_5$ requires C, 56·3; H, 2·7; N, 17·3%), from nitrobenzene. Treatment of the base with boiling acetic anhydride–pyridine gave the *acetyl derivative*, which crystallised from chloroform in needles, decomp. 300—304° (Found: N, 15·4. $C_{21}H_{13}O_7N_5$ requires N, 15·65%).

2 : 7-*Diamino*-9-*anilinophenanthridine*.—9-Anilino-2 : 7-dinitrophenanthridine (2·2 g.) was added to a hot solution of stannous chloride dihydrate (20 g.) in concentrated hydrochloric acid (20 ml.); the solution was boiled for 30 min., cooled, and then cautiously poured into concentrated aqueous sodium hydroxide. Crystallisation of the base from aqueous acetone gave

2 : 7-*diamino*-9-*anilinophenanthridine* (1·45 g., 79%) in yellow plates, m. p. 225—226° (decomp.) (Found : C, 75·9; H, 5·9; N, 18·2. $C_{19}H_{16}N_4$ requires C, 76·0; H, 5·3; N, 18·7%). The *hydriodide* formed orange needles, m. p. 224—226° (decomp.), from water (Found : N, 12·6; I, 29·05. $C_{19}H_{16}N_4,HI,H_2O$ requires N, 12·55; I, 28·5%). The *triacetyl derivative*, prepared with acetic anhydride–pyridine at 100° and crystallised from pyridine–ether, had m. p. 300—304° (Found : C, 70·0; H, 5·4; N, 12·9. $C_{25}H_{22}O_3N_4$ requires C, 70·4% H, 5·2; N, 13·1%).

2 : 7-*Diamino*-9-p-*aminoanilinophenanthridine*, similarly prepared in 90% yield, separated from aqueous acetone in yellow plates, m. p. 244—245° (decomp.) (Found : C, 72·3; H, 5·3; N, 21·4. $C_{19}H_{17}N_5$ requires C, 72·4; H, 5·4; N, 22·2%). The *triacetyl derivative*, prepared with acetic anhydride–pyridine at 100°, separated from acetone in needles, m. p. 328—329° (decomp.) (Found : C, 66·7; H, 5·3; N, 15·6; loss of wt. at 100°/15 mm., 2·5; regain in air, 2·5. $C_{25}H_{23}O_3N_5,0·5H_2O$ requires C, 66·7; H, 5·4; N, 15·55; H_2O, 2·0%). The *tetra-acetyl derivative*, formed when the base was boiled with acetic anhydride–pyridine, crystallised from aqueous pyridine in prisms, decomp. *ca.* 360° (Found : C, 63·1; H, 5·8; N, 13·5; loss of wt. at 100°/20 mm., 6·8. $C_{27}H_{25}O_4N_5,2H_2O$ requires C, 62·3; H, 5·6; N, 13·45; H_2O, 6·9%). The anhydrous compound re-formed the dihydrate in air.

2 : 7-*Di*(*ethoxycarbonylamino*)-9-p-*ethoxycarbonylaminoanilinophenanthridine*.—2 : 7-Diamino-9-*p*-aminoanilinophenanthridine (0·31 g.) in alcohol (50 ml.) was treated with diethylaniline (0·75 g.) and ethyl chloroformate (0·55 g.) and heated for 2 hr. under reflux at 100°. The solution was concentrated, the residual oil diluted with water and slightly acidified with hydrochloric acid, and the *hydrochloride* filtered off. Crystallisation from alcohol–ether gave yellow needles, m. p. 211—213° (decomp.) (Found : C, 56·8; H, 6·7; N, 12·25; Cl, 5·8; H_2O, 3·55. $C_{33}H_{39}O_6N_5,HCl,H_2O$ requires C, 57·4; H, 5·5; N, 11·9; Cl, 6·1; H_2O, 3·1%), partially hydrolysed by water with precipitation of the base. Crystallisation of the *base* from alcohol afforded needles, m. p. 238—242° (Found : C, 62·7; H, 5·6; N, 13·0. $C_{33}H_{39}O_6N_5$ requires C, 63·3; H, 5·5; N, 13·2%).

Reaction of Triacetyl-2 : 7-*diamino*-9-*anilinophenanthridine with Methyl Iodide*.—(*a*) The triacetyl derivative (0·6 g.), excess of methyl iodide, and methanol were heated under reflux for 18 hr., and the solution was then cooled. After 3 days the product (0·63 g.) was filtered off and crystallised from alcohol, giving yellow plates, m. p. 330—340° (decomp.) (Found : N, 10·5; I, 22·3; *N*-Me, 2·0. $C_{26}H_{25}O_3N_4I$ requires N, 9·85; I, 22·3; *N*-Me, 2·6%). When the salt was hydrolysed with boiling concentrated hydrochloric acid, iodine was evolved and 2 : 7-diamino-9-anilinophenanthridine, m. p. 224—226° (decomp.) (Found : C, 75·9; H, 5·4%), was recovered. Its m. p. was not depressed when it was mixed with an authentic specimen.

(*b*) The triacetyl derivative (0·4 g.) in excess of methyl iodide and methanol was heated for 18 hr. in a sealed tube at 110°. The product was filtered off and crystallised from water, yielding 2 : 7-bisdimethylaminophenanthridone bismethiodide dihydrate in yellow needles, m. p. 330° (decomp.) (Found : C, 38·7; H, 5·0; N, 7·35; I, 43·6; H_2O, 7·3; *N*-Me, 14·2; regain in air of anhydrous salt, 6·0. Calc. for $C_{19}H_{25}ON_3I_2,2H_2O$: C, 38·0; H, 4·85; N, 7·0; I, 42·3; H_2O, 6·0; *N*-Me, 15·0%).

Reaction of 2 : 7-*Diamino*-9-p-*aminoanilinophenanthridine and its Acetyl Derivatives with Methyl Iodide*.—(*a*) 2 : 7-Diamino-9-*p*-aminoanilinophenanthridine (0·35 g.) with methyl iodide–methanol at 115° gave 2 : 7-bisdimethylaminophenanthridone bismethiodide dihydrate (0·25 g.), m. p. 320—330° (decomp.) (Found : C, 38·4; H, 5·0; N, 7·0; I, 41·65; H_2O, 4·3; regain in air of anhydrous salt, 5·5%) [$\lambda_{max.}$ in 0·1N-HCl at 336 (ε 8300), 325 (ε 9830), and 260 mμ (ε 23,650); infl. at 269 mμ (ε 14,900)].

(*b*) The same salt, m. p. 310—325° (decomp.) (Found : N, 7·4; I, 43·5%), was obtained from the triacetyl derivative at 140°.

(*c*) The tetra-acetyl derivative was recovered substantially unchanged from boiling methyl iodide–methanol after 20 hr. At 110° the phenanthridone bismethiodide was formed, having m. p. 345° (decomp.) (Found : C, 37·9; H, 4·6; N, 7·45; I, 43·6%).

Reaction of 2 : 7-*Di*(*ethoxycarbonylamino*)-9-p-*ethoxycarbonylaminoanilinophenanthridine with Methyl Iodide*.—The trisurethane (0·53 g.) and anhydrous sodium carbonate (0·05 g.) were boiled for 13 hr. with excess of methyl iodide in alcohol. The red solution was evaporated and the residue was crystallised twice from acetone–ether, yielding 2 : 7-*di*(*ethoxycarbonylamino*)-9-(*N-methyl*-p-*ethoxycarbonylaminoanilino*)*phenanthridine hydriodide*, m. p. 250—255° (decomp.) (Found : C, 10·3; I, 18·4; OEt, 20·1; *N*-Me, 1·2. $C_{29}H_{31}O_6N_5,HI$ requires N, 10·4; I, 18·8; OEt, 20·1; *N*-Me, 2·2%). The *base*, purified from aqueous alcohol, appeared to be amorphous; it had m. p. 210—220° (decomp.) (Found : C, 63·4; H, 5·8; N, 12·5. $C_{29}H_{31}O_6N_5$ requires C, 63·8; H, 5·7; N, 12·8%).

Reduction of 9-Chloro-2 : 7-dinitrophenanthridine.—The dinitro-compound (0·25 g.) and platinum oxide (0·1 g.) in dioxan (50 ml.) were shaken with hydrogen at atmospheric temperature and pressure; the uptake was 160 ml. in 30 min. The yellow solution (green fluorescence) was filtered and evaporated and the residue was crystallised from acetone–benzene, giving yellow prisms, decomp. >200° (Found: N, 16·9; Cl, 14·3. Calc. for $C_{13}H_{10}N_2Cl$: N, 17·2; Cl, 14·6. Calc. for $C_{13}H_{12}N_2Cl$: N, 17·1; Cl, 14·3%). The diamino-chloro-compound was soluble in dilute hydrochloric acid and was precipitated unchanged by alkali.

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70. *The Kinetics of the Reaction between Cobalt*(III) *and Thallium*(I) *in Aqueous Perchloric Acid.*

By K. G. Ashurst and W. C. E. Higginson.

Kinetic experiments have shown that the principal reaction path in the reduction of cobalt(III) by thallium(I) in aqueous perchloric acid is independent of the hydrogen-ion concentration under the conditions chosen. The activation energy and temperature-independent factor have been found. The catalysis of this system by sulphate ions has been studied briefly.

In solution in dilute aqueous perchloric acid, cobalt(III) is reduced by thallium(I), $2Co(III) + Tl(I) \longrightarrow 2Co(II) + Tl(III)$, and the kinetics of this reaction can be followed conveniently by titration of cobalt(III) in samples taken at appropriate times. Thallium(III) reacts slowly with many reducing agents, so the estimation of cobalt(III) in reaction solutions is comparatively simple. The concentration conditions for kinetic experiments must be chosen carefully since cobalt(III) decomposes in solution with the formation of cobalt(II) and oxygen.[1] Under conditions similar to those in our experiments, this reaction is of between first and second order in cobalt(III),[2] while in the presence of thallium(I) our preliminary experiments showed that the rate of disappearance of cobalt(III) was of first order in both species. By use of the lowest initial concentrations of cobalt(III) compatible with sufficiently accurate analysis for our purposes, and relatively high thallium(I) concentrations, the rate of the decomposition can be reduced to less than 10% of the total rate of disappearance of cobalt(III) in most experiments, but the study of the cobalt(III)–thallium(I) reaction is thus restricted to experiments in which thallium(I) is in considerable excess. Initial concentrations were 0·74—3·1 $\times 10^{-3}$M-cobalt(III) and 9·7—65·0 $\times 10^{-3}$M-thallium(I).

The influence of the products upon the rate of reaction was investigated. Thallium(III), in concentration 15 times greater than that formed by the reaction, caused a slight increase in rate. This effect was not studied further but may have been due to the presence of thallium(I) as impurity in a thallium(III) stock solution. Cobalt(II), in relatively high concentration, caused a decrease in rate as shown in Fig. 1, in which concentrations of cobalt(III) are plotted against time for two experiments at 25°. In this respect the reaction resembles the oxidation of iron(II) by thallium(III), in which iron(III) exerts a retarding effect.[3] From this qualitative evidence we conclude that the reaction mechanism can be represented by

$$Co(III) + Tl(I) \longrightarrow Co(II) + Tl(II) \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$Co(II) + Tl(II) \longrightarrow Co(III) + Tl(I) \quad . \quad . \quad . \quad . \quad . \quad . \quad (-1)$$

$$Co(III) + Tl(II) \longrightarrow Co(II) + Tl(III) \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

[1] Bawn and White, *J.*, 1951, 331.
[2] Baxendale and Wells, unpublished work.
[3] Ashurst and Higginson, *J.*, 1953, 3044.

the retardation by cobalt(II) occurring through reaction (−1). This conclusion is more tentative than that reached in studying the iron(II)–thallium(III) reaction, where it was possible to evaluate the ratio of the rate constants for the reactions: Fe(III) + Tl(II) ⟶ Fe(II) + Tl(III), and Fe(II) + Tl(II) ⟶ Fe(III) + Tl(I), which correspond to (−1) and (2) above. In the cobalt(III)–thallium(I) system, however, our results are not sufficiently accurate to enable the ratio of the rate constants of reactions (−1) and (2) to be found.

Cobalt(II) occurs as an impurity in the cobalt(III) sulphate used, and in most experiments the initial cobalt(II) concentration was between 25% and 50% of the total cobalt concentration, *i.e.*, of the order 10^{-3}M-cobalt(II). Variations of this magnitude

FIG. 1. *Initial concns.*: (●) 65·0 × 10^{-3}M-*thallium*(I), 2·50M-*hydrogen-ion, and* 1·12 × 10^{-3}M-*cobalt*(II); (▲) 21·5 × 10^{-3}M-*cobalt*(II).

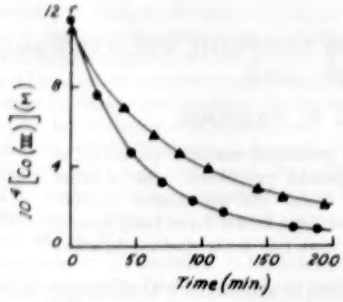
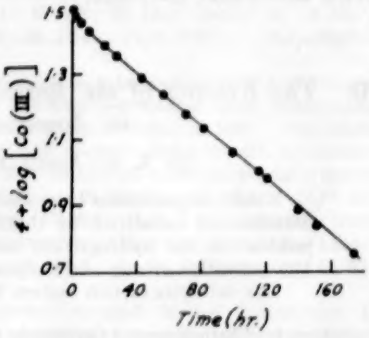


FIG. 2.



in the initial cobalt(II) concentration caused no systematic change in the rate of reaction and, since the rate is only halved with 25 × 10^{-3}M-cobalt(II), we conclude that with *ca.* 10^{-3}M-cobalt(II) the retarding effect can be neglected. Consequently, the rate of disappearance of cobalt(III) depends only on reaction (1) at low cobalt(II) concentrations, and the rate constant for this reaction, k_1, defined by $-d[Co(III)]/dt = 2k_1[Co(III)][Tl(I)]$, can be evaluated. The dependence of k_1 upon the hydrogen-ion concentration over the range 0·25—2·50M was investigated at 0°, 7·5°, 15°, and 25°, at ionic strength 2·70. In all these experiments, summarised in Table 1, thallium(I) was in considerable excess,

TABLE 1.

Expt.	10^3 × Initial concns. (M) $[H^+]$	Co(III)	Co(II)	Tl(I)	$100k_1$ (l. mole^{-1} min.$^{-1}$)	Expt.	10^3 × Initial concns. (M) $[H^+]$	Co(III)	Co(II)	Tl(I)	$100k_1$ (l. mole^{-1} min.$^{-1}$)
		At 0°					At 15°				
16	2·00	1·25	0·47	23·3	0·316	27	2·50	0·91	0·61	22·4	4·47
17	1·00	1·24	0·48	29·2	0·344	12	2·00	1·93	1·51	25·2	4·34
18	1·00	3·11	1·05	29·9	0·272	13 [a]	2·00	1·94	1·49	25·2	5·02
19	0·52	3·14	1·02	29·9	0·270	28	2·00	0·96	0·56	48·2	4·54
20	0·52	1·23	0·48	29·2	0·320	29	1·50	0·98	0·54	48·2	4·61
21	0·37	1·23	0·49	29·2	0·378	30	1·00	1·00	0·52	48·2	4·74
22	0·25	1·23	0·49	29·2	0·468	31	0·70	1·45	1·45	47·7	5·39
						32	0·50	0·98	0·53	48·4	5·21
		At 7·5°				33	0·50	1·08	0·74	47·7	5·16
23	2·00	1·26	0·46	38·9	1·07	34	0·50	1·08	0·74	47·7	5·21
24	1·00	1·25	0·47	38·9	1·05	35	0·37	0·84	0·77	48·2	6·10
25	0·52	1·25	0·47	38·9	1·10	36	0·25	0·83	0·69	48·2	7·08
26	0·30	1·24	0·47	38·9	1·14	37	0·25	0·92	0·83	47·7	6·74
						38	0·10	0·74	0·87	48·2	8·46
		At 25°				39	0·10	0·95	0·80	47·7	8·19
14	2·00	1·19	0·53	9·7	15·4						
15 [b]	2·00	1·19	0·53	9·7	18·2						
40	2·00	1·13	0·59	29·2	15·7						
41	0·70	1·08	0·64	29·2	16·0						
42	0·37	0·99	0·73	38·9	17·0						
43	0·25	0·99	0·73	38·9	19·0						

[a] [Tl(III)] = 0·0157M.
[b] [Tl(III)] = 0·0079M.

and plots of log Co(III) against time were nearly linear. Fig. 2 shows such a plot for Expt. no. 19. As can be seen from this plot, the initial rate of disappearance of cobalt(III) was more rapid than would be observed if first-order kinetics held throughout. This effect was particularly noticeable in experiments at lower hydrogen-ion concentrations, and we think it may be caused by the reaction of dimeric cobalt(III) ions which are probably present under these conditions. Reference to Table 1 shows that at each temperature the variation in rate constant with hydrogen-ion concentration is comparatively small, showing that a reaction path independent of the hydrogen-ion concentration predominates under these conditions. Although there is no accurate measurement of the first acidity constant of the cobalt(III) ion, $K = [CoOH^{2+}]\,[H^+]/[Co^{3+}]$, Baxendale and Wells[2] conclude that $K \ll 5 \times 10^{-3}$ mole l.$^{-1}$, and hence in our experiments the extent of hydrolysis is small. We have therefore assumed that the variation of k_1 at a given temperature can be represented by $k_1 = k_1' + k_1''K/[H^+]$. Our results are not sufficiently accurate to provide a

FIG. 3.

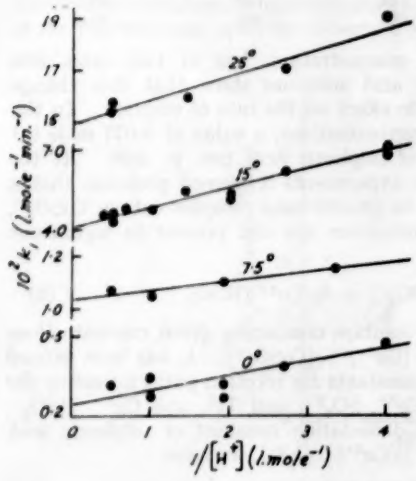
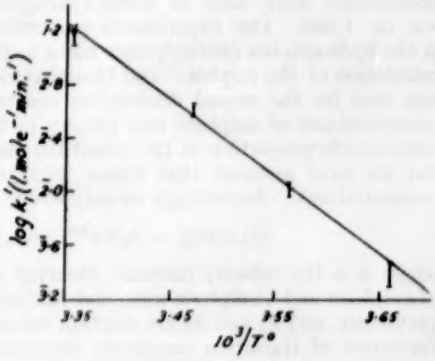


FIG. 4.



good test of this assumption, but as shown in Fig. 3, in which k_1 is plotted against $1/[H^+]$ for each temperature, a reasonably satisfactory extrapolation to infinite hydrogen-ion concentration is obtained, allowing k_1' to be determined. Values of $100k_1'$ deduced from these plots are 0·25 ± 0·05, 1·04 ± 0·10, 4·1 ± 0·4, and 15·0 ± 1·5 l. mole^{-1} min.$^{-1}$ at 0°, 7·5°, 15°, and 25°. We do not consider that good values of Kk_1'' can be obtained from the slopes of these plots. However, a value of 5×10^{-3} mole l.$^{-1}$ being assumed for K, k_1'' is of the order unity (l. mole^{-1} min.$^{-1}$ units) at 15°.

For each experiment in Table 1 a control was done simultaneously in the absence of thallium(I), the same freshly prepared cobalt(III) perchlorate solution being used, and other conditions being similar. We hoped to use the rate of the cobalt(III) decomposition reaction found in this way to correct the rate of disappearance of cobalt(III) in the presence of thallium(I) to give the true rate of the cobalt(III)–thallium(I) reaction. Under our conditions the cobalt(III) decomposition reaction is poorly reproducible and so we do not feel justified in making this correction. The control experiments show, however, that at hydrogen-ion concentrations of 0·5M or greater at 7·5°, 15°, and 25° the decomposition reaction contributes less than 10% to the total rate. At 0° the corresponding proportion is 15%. The values of k_1' quoted above may be too large by up to these amounts; for our purposes this error is not important. Fig. 4 shows the Arrhenius plot for k_1' (in l. mole^{-1} min.$^{-1}$) from which we find an activation energy of 26·4 ± 2·0 kcal. mole^{-1}, and a temperature-independent factor of $10^{(13\cdot6 \pm 1\cdot5)}$ l. mole^{-1} min.$^{-1}$.

Catalysis in Sulphate Solutions.—In the presence of sulphate ions the rate of reduction of cobalt(III) by thallium(I) is increased and this catalysis was investigated briefly in experiments at 15° and ionic strength 2·70, summarised in Table 2. Most of these

TABLE 2.

$[Tl(I)] = 0{\cdot}0482$M. Temp. = 15°.

	Initial concns. (M × 10^{-3})					
Expt.	$[H^+]$ (M)	Co(III)	Co(II)	$10^3[HSO_4^-]$ (M)	$10^4[SO_4^{2-}]$ (M)	$100k_s$ (l. mole^{-1} min.$^{-1}$)
44	2·50	1·06	0·45	2·7	0·83	4·26
45	2·48	1·24	0·48	121	37	5·34
46	2·49	1·26	0·46	246	76	8·00
47	2·48	1·06	0·45	272	84	7·87
48	2·49	1·18	0·57	490	152	11·1
49	2·49	1·08	0·43	514	159	10·6
50	2·49	1·05	0·46	757	234	12·6
51	2·50	1·03	0·48	1006	310	14·3
52	1·24	1·21	0·54	494	307	13·7
53	2·49	1·06	20·4	514	159	10·3
54	1·29	1·14	0·58	993	592	20·0

experiments were done at 2·50M-hydrogen-ion concentration, but in two cases this was *ca.* 1·25M. Our experiments in perchloric acid solutions show that this change in the hydrogen-ion concentration has a negligible effect on the rate of reaction. In the calculation of the sulphate- and bisulphate-ion concentrations, a value of 0·077 mole l.$^{-1}$ was used for the second dissociation constant of sulphuric acid (see p. 349). At the concentrations of sulphate ions present in these experiments it seemed probable that a considerable proportion of the cobalt(III) might be present as a complex cation, $CoSO_4^+$, but we have assumed that higher sulphate complexes are not present in significant concentrations. Accordingly we may write,

$$k_s[Co(III)] = k_1[Co^{3+}] + k_A[CoSO_4^+] + k_B[Co^{3+}][HSO_4^-] \quad . \quad . \quad . \quad (3)$$

where k_s is the velocity constant observed in a solution containing given concentrations of sulphate and bisulphate ions, and $[Co(III)] = [Co^{3+}] + [CoSO_4^+]$. k_1 has been defined previously, and k_A and k_B are reaction velocity constants for reaction paths involving the formation of transition complexes containing Co^{3+}, SO_4^{2-}, and Tl^+, and Co^{3+}, HSO_4^-, and Tl^+ respectively. Introducing the second dissociation constant of sulphuric acid, K_2, and the association constant $K_A = [CoSO_4^+]/[Co^{3+}][SO_4^{2-}]$, we have

$$k_s = k_1/(1 + K_A[SO_4^{2-}]) + k_AK_A[SO_4^{2-}]/(1 + K_A[SO_4^{2-}]) + k_B[H^+][SO_4^{2-}]/K_2(1 + K_A[SO_4^{2-}]) \quad . \quad . \quad (4)$$

whence, by rearranging, we have,

$$1/(k_s - k_1) = (1 + 1/K_A[SO_4^{2-}])/\{k_A + (k_B[H^+]/K_AK_2) - k_1\} \quad . \quad . \quad (5)$$

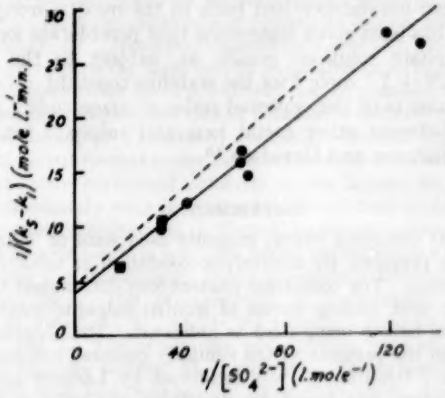
If the catalytic effect of sulphate can be treated in this way, a plot of $1/(k_s - k_1)$ as ordinate against $1/[SO_4^{2-}]$ should be linear, and enable the reciprocal of the term in the braces in (5) to be evaluated as the intercept on the y-axis, and K_A from this intercept and the gradient. Fig. 5 shows this plot based on the results of experiments in Table 2; the value of k_1 is taken from Expt. 44 in which the sulphate- and bisulphate-ion concentrations are relatively small. The plot does not include Expt. 45 which lies well off the full line. The error on this point is large and we do not consider that this deviation provides evidence against the validity of equation (5) which appears to be confirmed by the points from the remaining experiments. We find $(k_A + k_B[H^+]/K_AK_2) = 0{\cdot}29 \pm 0{\cdot}06$ l. mole^{-1} min.$^{-1}$, and $K_A = 22 \pm 7$ l. mole^{-1}.

It is evident from equation (5) that, unless k_B is zero, points from experiments at lower hydrogen-ion concentrations should lie on lines of greater intercept and gradient. Thus if k_B has a value of 0·05 l.^{2} mole^{-2} min.$^{-1}$, the points corresponding to Expts. 52 and 54 (shown as squares in Fig. 5) should lie on the broken line instead of the full line drawn through the remaining points, all of which correspond to experiments at a higher hydrogen-ion concentration. However, the squares lie fairly close to the full line, but are just

outside their estimated limits of error from the broken line. We conclude that k_B is not greater than 0·05 l.^{2} mole^{-2} min.$^{-1}$ and is probably considerably less. From this value of the upper limit for k_B the rate constant observed at 15° would be about four times greater in a 2·70M-bisulphate-ion solution, if it were possible to exclude sulphate ions, than in the 2·70M-perchlorate-ion solutions used in experiments in the absence of other anions. A value of zero for k_B implies that the replacement of perchlorate ions by equal concentrations of bisulphate ions has no effect on the rate of reaction. If k_B is zero, $k_A = 0{\cdot}29 \pm 0{\cdot}06$ l. mole^{-1} min.$^{-1}$, and if $k_B = 0{\cdot}05$ l.^{2} mole^{-2} min.$^{-1}$, $k_A = 0{\cdot}22 \pm 0{\cdot}06$ l. mole^{-1} min.$^{-1}$. It is clear that the catalysis observed on addition of sulphate ions is largely due to the fairly small concentrations of free sulphate ions, and that there is little increase in rate caused by the much larger concentrations of bisulphate ions inevitably present at the hydrogen-ion concentrations employed in our experiments. In the presence of sulphate ions it is noteworthy that the back-reaction, (−1), is relatively unimportant even at high cobalt(II) concentrations (compare Expts. 49 and 53).

Discussion.—In many oxidation–reduction reactions between simple metal ions, kinetic experiments show marked catalysis by negative ions of small radius, the dependence of the reaction rate upon the inverse hydrogen-ion concentration frequently encountered

FIG. 5.



being usually regarded as evidence for catalysis by hydroxyl ions. The probable rôle of such negative ions in reducing the repulsive forces between the metal cations, thus permitting their closer approach in the transition state and facilitating electron-transfer, has been emphasised.[4] In the reaction between cobalt(III) and thallium(I) our experiments show that the principal reaction path is independent of the hydrogen-ion concentration in perchlorate-ion solutions of hydrogen-ion concentration 0·25—2·50M, in contrast to reactions such as Np(IV) + Fe(III) ⟶ Np(V) + Fe(II),[5] and V(III) + Fe(III) ⟶ V(IV) + Fe(II).[6] In perchloric acid solutions there is evidence only for reaction paths showing dependence on an inverse function of the hydrogen-ion concentration in both these reactions. The charge products of the reacting metal ions, aud hence the electrostatic repulsion between them at a given separation, are much greater in these two reactions than in the cobalt(III)–thallium(I) reaction which is seen to be a more favourable case for observing a reaction path which does not involve small anions. Even in this case it is possible that perchlorate ions or, on account of the favourable polarity of their oxygen atoms, water molecules may act as bridging groups and reduce the considerable repulsion energy between the metal ions at distances where the probability of electron-transfer is significant. Unfortunately, our kinetic experiments cannot give any direct information

[4] Zwolinski, Marcus, and Eyring, *Chem. Rev.*, 1955, **55**, 157.
[5] Huizenga and Magnusson, *J. Amer. Chem. Soc.*, 1951, **73**, 3202.
[6] Higginson and Hughes, unpublished work.

regarding the incorporation of water molecules or perchlorate ions in the transition state corresponding to the hydrogen-ion-independent reaction path. However, the entropy of activation of this reaction can be calculated as 22 ± 7 cal. deg.$^{-1}$ mole^{-1} from the temperature-independent factor of $10^{(13\cdot6 \pm 1\cdot5)}$ l. mole^{-1} min.$^{-1}$ by using a value of 6×10^{13} l. mole^{-1} min.$^{-1}$ as the normal frequency factor. For a reaction between ions of like charge this large positive entropy of activation seems surprising but, if the transition complex includes one or more perchlorate anions, the loss of charge consequent on its formation should result in a positive entropy change owing to the release of water of solvation. Electron-transfer reactions have been classified according to whether their entropy of activation is positive or negative,[7] and in all the aqueous reactions cited where this entropy is positive the formation of the transition complex is known to involve a net loss of charge. In the reactions between two metal cations this loss of charge occurs through the incorporation of one or more negative ions in the transition complex. That relatively large anions may act as catalysts is shown in the cobalt(III)–thallium(I) reaction by the effect of sulphate ions, and in other reactions nitrate ions have been found effective.[8] Replacement of perchlorate by bisulphate ions has little effect on the rate of reaction, which is in accord with the similarity in size and charge of these two ions. We conclude therefore that there is indirect evidence in favour of the participation of perchlorate ions in the hydrogen-ion-independent cobalt(III)–thallium(I) reaction. In contrast, the entropy of activation is negative in the hydrogen-ion-independent path in the iron(II)–iron(III) electron-exchange reaction, and evidence has been given suggesting that perchlorate ions do not take part.[9]

The results in sulphate solutions enable us, subject to the assumptions implicit in equation (3), to find 22 ± 7 l. mole^{-1} for the stability constant of $CoSO_4^+$ at 15° and ionic strength 2·70. This value is of the expected order of magnitude; a list of concentration association constants between other metal ions and sulphate ions at fairly high ionic strengths is given by Whiteker and Davidson.[10]

Experimental

Materials.—Except as described below, reagents used were of "AnalaR" quality. Solid cobalt(III) sulphate was prepared by electrolytic oxidation of cobalt(II) sulphate,[11] and was stored at 0° in a desiccator. The cobalt(III) content was determined by dissolving a weighed amount in 2M-sulphuric acid, adding excess of iron(II) sulphate solution, and back-titrating with cerium(IV) sulphate, ferroin being used as indicator. The accuracy of the end-points, in titrations using ferroin in the presence of the similarly coloured cobalt(II) ion, was checked by potentiometric titration. Total cobalt was estimated by Latimer and Burdett's iodometric method.[12] The acid content was found by dissolving the solid in water whereupon rapid decomposition to cobalt(II) sulphate occurred. Titration with alkali and bromocresol-green as indicator then gave the hydrogen-ion content of the solid, allowance being made for hydrogen ions formed in the decomposition of cobalt(III) before titration, $4Co^{3+} + 2H_2O \longrightarrow 4Co^{2+} + 4H^+ + O_2$. The sulphate-ion content of the solid cobalt(III) sulphate, expressed as equiv. per g., was assumed to be equal to the sum of the cobalt(III), cobalt(II), and hydrogen-ion contents, each being expressed as equiv. per g.

Thallium(I) perchlorate was obtained from pure thallium(I) nitrate by fuming with excess of 60% perchloric acid, and was recrystallised three times from water. A stock solution in water was made up by weight, and its strength checked by titration against standard potassium iodate in hydrochloric acid solution under Andrews's conditions.

Sodium perchlorate solution, used in making the ionic strength in kinetic experiments up to 2·70, was prepared by neutralising 60% perchloric acid with solid sodium hydroxide and filtering. Barium perchlorate solution was prepared similarly by using solid barium hydroxide octahydrate. Cobalt(II) perchlorate solution was prepared by double decomposition between a solution of cobalt(II) sulphate and the barium perchlorate solution.

Procedure in Kinetic Experiments.—In kinetic experiments in the absence of sulphate a

[7] Marcus, Zwolinski, and Eyring, *J. Phys. Chem.*, 1954, **58**, 432.
[8] Prestwood and Wahl, *J. Amer. Chem. Soc.*, 1949, **71**, 3137.
[9] Silverman and Dodson, *J. Phys. Chem.*, 1952, **56**, 846.
[10] Whiteker and Davidson, *J. Amer. Chem. Soc.*, 1953, **75**, 3085.
[11] Swann and Xanthakos, *ibid.*, 1931, **53**, 400.
[12] Latimer and Burdett, *Analyt. Chem.*, 1951, **23**, 1268.

weighed amount of cobalt(III) sulphate was dissolved in perchloric acid, and the sulphate ions removed by adding a slight excess of barium perchlorate solution. The solution was then filtered through No. 4 porosity sintered glass and a measured volume of the filtrate was added to the other constituents of the reaction mixture which had previously been measured into a 500-ml. stoppered flask. The remainder of the cobalt(III) perchlorate solution was used for a control experiment in absence of thallium(I) but at a similar hydrogen-ion concentration and ionic strength. In experiments in the presence of sulphate ions the solid cobalt(III) sulphate was dissolved in perchloric acid, and a measured volume added immediately to the other constituents of the mixture which included sodium sulphate or sulphuric acid. As before, the remainder of the cobalt(III) solution was used for a control experiment in absence of thallium(I).

Samples of the reaction mixture were removed at appropriate intervals of time, added to a small excess of iron(II) sulphate solution, and then titrated against 0·002M-cerium(IV) sulphate solution, with ferroin as indicator. The validity of this method for determining cobalt(III) in these solutions was confirmed by making up solutions of known composition, similar to those obtained during a reaction, and immediately determining cobalt(III) as described above. Attempts to quench the reaction by using cerium(III) instead of iron(II) gave inaccurate results, possibly owing to a slow reaction between cobalt(III) and cerium(III). In the few experiments at high thallium(III) concentrations it was necessary to cool the iron(II) sulphate quenching solution to 0° and perform the back-titration at this temperature to prevent oxidation of the iron(II) by thallium(III). The accuracy of these cobalt(III) concentration determinations was found to be $\pm 0{\cdot}8\%$ for 10^{-3}M- and $\pm 4\%$ for 10^{-4}M-cobalt(III) solutions.

It was not possible to conduct experiments in absence of oxygen since this gas is formed by the decomposition of cobalt(III). However, experiments in which pure nitrogen was bubbled through the reaction mixture gave the same results as parallel experiments in which the mixture was open to the air, and therefore we think it unlikely that oxygen has a significant effect on the rate. Other experiments showed that the rate of reaction is not affected by daylight.

Stoicheiometry of the Cobalt(III)–*Thallium*(I) *Reaction.*—Several experiments were done to find the amount of thallium(III) formed under the conditions of the kinetic experiments. These quantitative experiments were performed similarly to the kinetic experiments. The control solution was titrated immediately with iron(II) sulphate solution to find the initial cobalt(III) concentration, while the solution containing thallium(I) remained untouched until the completion of reaction. Sodium hydroxide solution was then added with stirring until the pH rose to about 3·5, as found by allowing the thallium(III) oxide precipitate to settle and testing the clear liquor with bromophenol-blue. The precipitation of thallium(III) oxide appeared to be substantially complete at about pH 2. At pH 3·5 cobalt(II) remains in solution,[13] and is not precipitated until about pH 7. The precipitate and solution were stirred for 24 hr. and then filtered through a No. 3 porosity sintered-glass crucible. The precipitate was washed rapidly with very dilute sulphuric acid, and then several times with water, dried *in vacuo* [$Mg(ClO_4)_2$], and weighed. The weight of thallium(III) oxide collected was about 80 mg. in each experiment, and corresponded to between 95% and 99% of the production of thallium(III) calculated from the amount of cobalt(III) present initially. We estimate the error in these figures to be $\pm 5\%$ and conclude that, with the exception of a small loss due to the decomposition of cobalt(III), the cobalt(III)–thallium(I) reaction is quantitative under our conditions.

Determination of the Second Dissociation Constant of Sulphuric Acid.—The value of this constant, $K_2 = [H^+][SO_4^{2-}]/[HSO_4^-]$, was required at ionic strength 2·70 and 15°, and was found by an optical method, picric acid being used as indicator. Optical measurements were made with a Unicam model SP500 quartz spectrophotometer; 4-cm. quartz cells were employed. A calibration curve of hydrogen-ion concentration against optical density at 358 mμ was found for 5×10^{-5}M-picric acid solutions in aqueous perchloric acid–sodium perchlorate mixtures of ionic strength 2·70. The range of hydrogen-ion concentration studied was 0·03—0·12M, and a solution of the latter concentration was used as the optical blank solution. The optical densities of 5×10^{-5}M-picric acid containing similar, known concentrations (not less than 0·1M) of sodium sulphate and sulphuric acid, and sufficient sodium perchlorate to bring the ionic strength to 2·70, were then determined. The corresponding hydrogen-ion concentrations were found from the calibration curve, enabling the second dissociation constant of sulphuric acid to be calculated. The mean value obtained from five experiments was $0{\cdot}077 \pm 0{\cdot}005$ mole $l.^{-1}$.

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[*Received, September 7th*, 1955.]

[13] Britton, *Ann. Reports*, 1943, **40**, 45.

71. *Synthesis of Polycyclic Compounds. Part I. A New Synthesis of Alkylphenanthrenes.*

By J. C. Bardhan and D. Nasipuri.

Ethyl 4 : 6-dioxoheptane-1 : 5-dicarboxylate was alkylated with a phenethyl bromide and the product (*e.g.*, III) cyclised with sulphuric acid to a naphthalene derivative (*e.g.*, IV); this was converted (Dieckmann) into a hydro-oxophenanthrene (*e.g.*, V), and thence by conventional methods into alkylphenanthrenes. A very flexible new route is thus available which is here used for preparation of several alkylphenanthrenes.

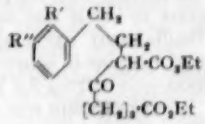
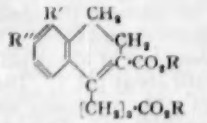
Synthetic 2-ethyl-1 : 8-dimethylphenanthrene was identical with the product, $C_{18}H_{18}$, of dehydrogenation of methyl vinhaticoate and related diterpenoids.[1]

Research, begun in 1936, on the preparation of hydrophenanthrene derivatives useful for the synthesis of œstrogenic ketones,[2] is now being resumed. Such of the earlier work as has not been published from other laboratories will now be reported.

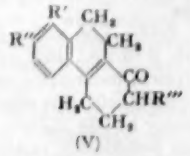
γ-Ethoxycarbonylbutyryl chloride with ethyl sodioacetoacetate gave mainly ethyl 4 : 6-dioxoheptane-1 : 5-dicarboxylate (I), converted by ethanolic sodium ethoxide into ethyl β-oxopimelate (II), albeit in unsatisfactory yield.[3] Nevertheless, the sodio-derivative

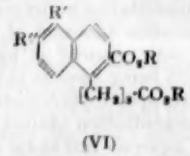
$$EtO_2C\cdot[CH_2]_3\cdot COCl \longrightarrow \underset{(I)}{EtO_2C\cdot[CH_2]_3\cdot CO\cdot CHAc\cdot CO_2Et} \longrightarrow \underset{(II)}{EtO_2C\cdot[CH_2]_3\cdot CO\cdot CH_2\cdot CO_2Et}$$

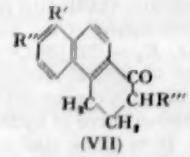
is doubtless formed satisfactorily, for treatment with phenethyl bromide without isolation of the ester (II) afforded a good yield of ethyl β-oxo-α-phenethylpimelate (III; R′ = R″ = H) (for similar reaction see Bouveault and Bongart [4]), which was converted into γ-(2-carboxy-3 : 4-dihydro-1-naphthyl)butyric acid (IV; R = R′ = R″ = H) by means of concentrated sulphuric acid. The derived diethyl ester, on condensation by means of sodium and hydrolysis, gave 1 : 2 : 3 : 4 : 9 : 10-hexahydro-1-oxophenanthrene [5] (V; R′ = R″ = R‴ = H), which was reduced by Clemmensen's method and then dehydrogenated

(III)   (IV)

with selenium to yield phenanthrene.[2] The ester (IV; R = Et, R′ = R″ = H) on dehydrogenation with sulphur and subsequent hydrolysis gave γ-(2-carboxy-1-naphthyl)-butyric acid (VI; R = R′ = R″ = H), converted by acetic anhydride into 1 : 2 : 3 : 4-tetrahydro-1-oxophenanthrene [6] (VII; R′ = R″ = R‴ = H).


(V)


(VI)


(VII)

By use of 2-*m*-tolylethyl bromide [7] these reactions led to the phenanthrene derivative (VII; R′ = R‴ = H, R″ = Me). 1 : 2 : 3 : 4 : 9 : 10-Hexahydro-7-methyl-1-oxophenanthrene (V; R′ = R‴ = H, R″ = Me) was condensed with methylmagnesium iodide,

[1] (*a*) King and King, *J.*, 1953, 4158; (*b*) King, Godson, and King, *J.*, 1955, 1118.
[2] Bardhan, *Chem. and Ind.*, 1936, 879.
[3] Cf. Birkofer and Storch, *Chem. Ber.*, 1953, **86**, 32; Loewenthal, *J.*, 1953, 3965.
[4] Bouveault and Bongart, *Bull. Soc. chim.*, 1902, **27**, 1100.
[5] Cf. : (*a*) Johnson, Johnson, and Peterson, *J. Amer. Chem. Soc.*, 1946, **68**, 1926; (*b*) Birch and Smith, *J.*, 1951, 1887.
[6] Cf. Haworth, *J.*, 1932, 1130.
[7] Shoesmith and Connor, *J.*, 1927, 1770; Carré, *Compt. rend.*, 1912, **148**, 1109.

and the resultant alcohol dehydrated with anhydrous formic acid and converted by selenium into 1 : 7-dimethylphenanthrene.[8] The tetrahydro-derivative (VII; R′ = R‴ = H, R″ = Me) likewise reacted with an excess of ethylmagnesium bromide affording, by the above reactions, 1-ethyl-7-methylphenanthrene.[8a, 9]

Similarly use of 2-*o*-tolylethyl bromide[8c] yielded 1 : 2 : 3 : 4 : 9 : 10-hexahydro-8-methyl-1-oxophenanthrene (V; R′ = Me, R″ = R‴ = H) and thence 1-ethyl-8-methylphenanthrene, identical with the product recently described by King and King.[10]

The ethyl ester (IV; R = Et, R′ = Me, R″ = H) was condensed by means of sodium, and the resultant product was ethylated and hydrolysed to give 2-ethyl-1 : 2 : 3 : 4 : 9 : 10-hexahydro-8-methyl-1-oxophenanthrene (V; R′ = Me, R″ = H, R‴ = Et), converted by reaction with methylmagnesium iodide, dehydration, and dehydrogenation into 2-ethyl-1 : 8-dimethylphenanthrene. The properties of this hydrocarbon and its picrate and trinitrobenzene derivative corresponded with those recorded for the ethyldimethylphenanthrene and its derivatives which King and King [1] obtained from methyl vinhaticoate, and the constitution suggested by these authors is thereby confirmed.

Lastly, the preceding ester was converted into 1 : 2 : 3 : 4-tetrahydro-8-methyl-1-oxophenanthrene [13] (VII; R′ = Me, R″ = R‴ = H), 1 : 2 : 3 : 4-tetrahydro-8-methyl-1-oxo-2-*iso*propylphenanthrene (VII; R′ = Me, R″ = H, R‴ = Pr^i), and 1 : 2 : 3 : 4-tetrahydro-2 : 8-dimethyl-1-oxophenanthrene [14] (VII; R′ = R‴ = Me, R″ = H), by the methods described for similar cases. The ketone (VII; R′ = Me, R″ = H, R‴ = Pr^i) was reduced by Clemmensen's method and the product dehydrogenated, to yield 1-methyl-7-*iso*propylphenanthrene.[8a, 9] The other two ketones on reaction with *iso*propylmagnesium bromide, under the usual conditions, gave 1-methyl-8-*iso*propyl- [11] and 2 : 8-dimethyl-1-*iso*propylphenanthrene respectively. The last compound differs from a hydrocarbon to which Short and Wang [12] ascribed this formulation.

Experimental

Condensation of γ-Ethoxycarbonylbutyryl Chloride with Ethyl Sodioacetoacetate.—A solution of γ-ethoxycarbonylbutyryl chloride (89 g.) in ether (200 ml.) was added slowly with cooling to a stirred slurry of ethyl sodioacetoacetate [from pulverised sodium (11·5 g.), ethyl acetoacetate (65 ml.), and dry ether (650 ml.)] and set aside overnight, then refluxed for 0·5 hr., and treated with 3N-sulphuric acid (300 ml.) with cooling and stirring. The ethereal extract was washed with water, dried (Na_2SO_4), and distilled. *Ethyl* 4 : 6-*dioxoheptane*-1 : 5-*dicarboxylate* (I) (90 g.), b. p. 152—153°/3 mm., was collected. A middle fraction was analysed (Found: C, 57·1; H, 7·3. $C_{13}H_{20}O_6$ requires C, 57·3; H, 7·4%). The ester which gives a red colour with aqueous-ethanolic ferric chloride is probably contaminated with the corresponding *O*-acyl ester.

Attempts to prepare Ethyl β-Oxopimelate (II).—The preceding ester (9 g.) was added to an ice-cold solution from sodium (0·75 g.) in absolute ethanol (15 ml.), and the resulting solution kept overnight at room temperature, whereafter water and excess of dilute sulphuric acid were added and the oil was collected in ether. On distillation it gave fractions: (*a*) b. p. 140°/4 mm. (5 g.); (*b*) b. p. 146—156°/4 mm. (2·5 g.). Fraction (*a*) showed an intense ferric reaction and was pure ethyl β-oxopimelate [3] (Found: C, 57·2; H, 7·8. Calc. for $C_{11}H_{18}O_5$: C, 57·4; H, 7·8%).

Ethyl β-Oxo-α-phenethylpimelate (III; R′ = R″ = H).—To an ice-cold solution of sodium ethoxide [from sodium (2·3 g.) and absolute ethanol (40 ml.)] was gradually added, with shaking, ethyl 4 : 6-dioxoheptane-1 : 5-dicarboxylate (27·2 g.). Next morning phenethyl bromide (18·5 g.) was added and the whole heated under reflux at 90—92° for 20 hr. It was then diluted with water, acidified, and repeatedly extracted with ether. The ethereal solution was washed with water, dried (Na_2SO_4), and evaporated. *Ethyl β-oxo-α-phenethylpimelate* formed a colourless liquid (15 g.), b. p. 190—193°/4 mm. (Found: C, 68·1; H, 7·8. $C_{19}H_{26}O_5$ requires C, 68·3; H, 7·8%), giving a red colour with ethanolic ferric chloride.

[8] (*a*) Ruzicka and Ballas, *Helv. Chim. Acta*, 1923, **6**, 677; 1924, **7**, 875; (*b*) Haworth, Letsky, and Mavin, *J.*, 1932, 1785; (*c*) Bardhan and Sengupta, *J.*, 1932, 2522.
[9] Haworth, *J.*, 1932, 2719.
[10] King and King, *J.*, 1953, 4167; 1954, 1373.
[11] Short and Wang, *J.*, 1950, 991.
[12] *Idem*, *J.*, 1951, 2980.
[13] Haworth, Mavin, and Sheldrick, *J.*, 1934, 458.
[14] Haworth and Mavin, *J.*, 1932, 2720.

γ-(2-Carboxy-3 : 4-dihydro-1-naphthyl)butyric Acid (IV; R = R′ = R″ = H).—The preceding keto-ester (5 g.) was slowly added with stirring to sulphuric acid (*d* 1·84; 30 ml.) at −10°. Stirring was continued for 3 hr. and then the mixture was poured on ice. The semisolid mass which separated was collected in ether, and the solution washed with water, dried, and evaporated. The brown residue was hydrolysed with potassium hydroxide (3 g.), water (3 ml.), and ethanol (30 ml.). The crude *acid* (3 g.) was purified by repeated crystallisation from dilute acetic acid (charcoal) and formed prisms, m. p. 138° (Found : C, 69·3; H, 6·2. $C_{15}H_{16}O_4$ required C, 69·2; H, 6·1%). The *diethyl ester* had b. p. 194—195°/3 mm. (Found : C, 71·9; H, 7·2. $C_{19}H_{24}O_4$ requires C, 72·1; H, 7·5%).

1 : 2 : 3 : 4 : 9 : 10-Hexahydro-1-oxophenanthrene (V; R′ = R″ = R‴ = H).—The preceding ester (3·1 g.) was heated with powdered sodium (0·23 g.) and dry benzene (8 ml.). The reaction which proceeded smoothly at 100° was completed in 2 hr. The viscous mass was decomposed with ice and dilute hydrochloric acid. The benzene extract was separated, washed with sodium carbonate solution, and dried, and the solvent removed under reduced pressure. The residual oil (3 g.) was hydrolysed by heating it with acetic acid (12 ml.) and concentrated hydrochloric acid (6 ml.) for 12 hr. The ketone (V; R′ = R″ = R‴ = H) (1·2 g.) had b. p. 168°/3 mm., m. p. 49° [from light petroleum (b. p. 40—60°)] (Found : C, 84·7; H, 7·1. Calc. for $C_{14}H_{14}O$: C, 84·8; H, 7·0%) (Johnson *et al.*[84] record m. p. 49—50°, and Birch and Smith [85] m. p. 48—49°). The semicarbazone separated in prisms (from ethanol), m. p. 254—255° (decomp.) in agreement with Bardhan ; [2] Johnson *et al.*[84] give m. p. 257—258°, and Birch and Smith [85] 250—251°.

Phenanthrene.—The foregoing ketone (2 g.) was reduced by Clemmensen procedure to an oil (1·2 g.) which was heated with selenium (2·5 g.) at 300—320° for 20 hr. The product was purified from ethanol (charcoal) and had m. p. 100° alone or mixed with phenanthrene (Found : C, 94·2; H, 5·5. Calc. for $C_{14}H_{10}$: C, 94·4; H, 5·7%).

γ-(2-Carboxy-1-naphthyl)butyric Acid (VI; R = R′ = R″ = H).—The dihydro-ester (IV; R = Et, R′ = R″ = H) (3·1 g.) was heated with powdered sulphur (0·32 g.) at 240—250° for 2 hr., and on distillation in a vacuum gave an oil (3 g.), b. p. 200—205°/4 mm. This on hydrolysis with ethanolic potassium hydroxide in the usual way afforded *γ-(2-carboxy-1-naphthyl)butyric acid* as needles (from aqueous ethanol), m. p. 167° [Found : C, 69·9; H, 5·4%; equiv., 129·0. $C_{15}H_{14}O_4$ (dibasic) requires C, 69·7; H, 5·4%; equiv., 129·0].

1 : 2 : 3 : 4-Tetrahydro-1-oxophenanthrene (VII; R′ = R″ = R‴ = H).—The foregoing acid (2 g.) was heated with redistilled acetic anhydride (7 ml.) for 3 hr., the excess of anhydride removed, and the residue distilled in a vacuum. The ketone [9] (VII; R′ = R″ = R‴ = H) separated from light petroleum (b. p. 60—80°) as plates, m. p. 95° (Found : C, 85·7; H, 6·2. Calc. for $C_{14}H_{12}O$: C, 85·7; H, 6·1%).

5-Oxo-8-phenyloctanoic Acid.—Ethyl β-oxo-α-phenethylpimelate (III; R′ = R″ = H) (5 g.) was refluxed for 10 hr. in concentrated hydrochloric acid (10 ml.) and acetic acid (20 ml.). The mixture was diluted with water, and the excess of acetic acid removed at 100° as completely as possible and the oil collected in ether. The *keto-acid* (3 g.) had b. p. 205—210°/3 mm. (Found : C, 71·6; H, 7·7. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). The *semicarbazone* had m. p. 126° (from ethanol) (Found : C, 61·7; H, 7·2. $C_{15}H_{21}O_3N_3$ requires C, 61·9; H, 7·2%). The *ethyl ester* had b. p. 165°/3 mm. (Found : C, 73·2; H, 8·4. $C_{16}H_{22}O_3$ requires C, 73·3; H, 8·4%).

2-Phenethylcyclohexane-1 : 3-dione.—The above ester (5 g.) was heated on the steam-bath with a solution from sodium (0·5 g.) in calcium-dried ethanol (20 ml.) for 20 hr. On cooling, the mixture was diluted with water and extracted with ether. The alkaline solution on acidification afforded the diketone [85] which crystallised from ethyl acetate–light petroleum (b. p. 60—80°) as plates, m. p. 147° (Found : C, 77·5; H, 7·4. Calc. for $C_{14}H_{16}O_2$: C, 77·8; H, 7·4%).

Ethyl β-Oxo-α-(2-m-tolylethyl)pimelate (III; R′ = H, R″ = Me).—This *ester* was prepared by the condensation of 2-*m*-tolylethyl bromide (20 g.) with ethyl 4 : 6-dioxoheptane-1 : 5-dicarboxylate (27·2 g.) in presence of a solution from sodium (2·3 g.) in absolute ethanol (40 ml.) as described above and had b. p. 190—193°/3 mm. (19 g.) (Found : C, 68·9; H, 8·1. $C_{20}H_{28}O_5$ requires C, 69·0; H, 8·0%).

γ-2-(Carboxy-7-methyl-3 : 4-dihydro-1-naphthyl)butyric Acid (IV; R = R′ = H, R″ = Me).—The preceding keto-ester (32 g.) on cyclisation with sulphuric acid gave the *acid* (IV; R = R′ = H, R″ = Me) (18 g.), prisms, m. p. 154—155° (from aqueous acetic acid) [Found : C, 70·0; H, 6·6%; equiv., 137·0. $C_{16}H_{16}O_4$ (dibasic) requires C, 70·0; H, 6·6%; equiv., 137·0]. The *ethyl ester* boiled at 195°/3 mm. (Found : C, 72·6; H, 8·0. $C_{20}H_{26}O_4$ requires C, 72·7; H, 7·9%).

1 : 2 : 3 : 4 : 9 : 10-*Hexahydro*-7-*methyl*-1-*oxophenanthrene* (V; R′ = R‴ = H, R″ = Me).—The ester (IV; R = Et, R′ = H, R″ = Me) on Dieckmann cyclisation and hydrolysis in the usual way afforded the *ketone* (V; R′ = R‴ = H, R″ = Me), b. p. 160—163°/3 mm. (Found: C, 85·2; H, 7·6. $C_{15}H_{16}O$ requires C, 85·0; H, 7·5%). The *semicarbazone* formed plates (from ethanol), m. p. 254—255° (decomp.) (Found: C, 71·2; H, 7·2. $C_{16}H_{19}ON_3$ requires C, 71·4; H, 7·1%).

1 : 7-*Dimethylphenanthrene* (***Pimanthrene***).—A solution of the preceding ketone (2 g.) in dry ether (30 ml.) was added dropwise at room temperature to methylmagnesium iodide [from magnesium (1 g.), methyl iodide (3 ml.), and dry ether (32 ml.)]. The mixture was refluxed for 4 hr. The product (2 g.) was isolated in the usual way and heated on the water-bath with anhydrous formic acid (4 ml.) for 0·5 hr. and on distillation yielded an oil (1·7 g.), b. p. 155°/3 mm. This on dehydrogenation with selenium (3·5 g.) at 300—320° for 30 hr. gave 1 : 7-dimethylphenanthrene, plates, m. p. 86° (from ethanol) (Found: C, 93·2; H, 6·8. Calc. for $C_{16}H_{14}$: C, 93·2; H, 6·8%). The picrate crystallised from ethanol in needles, m. p. 132° (Found: C, 60·4; H, 4·0. Calc. for $C_{16}H_{14},C_6H_3O_7N_3$: C, 60·7; H, 3·9%).[8a,b]

γ-(2-*Carboxy*-7-*methyl*-1-*naphthyl*)*butyric Acid* (VI; R = R′ = H, R″ = Me).—This was prepared by the dehydrogenation of ethyl γ-(2-ethoxycarbonyl-7-methyl-3 : 4-dihydro-1-naphthyl)butyrate (IV; R = Et, R′ = H, R″ = Me) with sulphur in the usual way. The *acid* crystallised from methanol in prisms, m. p. 188—190° (Found: C, 70·2; H, 5·8. $C_{16}H_{16}O_4$ requires C, 70·5; H, 5·9%). The *ethyl ester* had b. p. 198—200°/3 mm. (Found: C, 73·1; H, 7·3. $C_{20}H_{24}O_4$ requires C, 73·2; H, 7·3%).

1 : 2 : 3 : 4-*Tetrahydro*-7-*methyl*-1-*oxophenanthrene* (VII; R′ = R‴ = H, R″ = Me).—Cyclisation of the preceding ester with sodium gave the *ketone*, b. p. 175—178°/3 mm., needles, m. p. 71° [from light petroleum (b. p. 40—60°)] (Found: C, 85·8; H, 6·6. $C_{15}H_{14}O$ requires C, 85·7; H, 6·7%). The *semicarbazone* (from ethanol) melts at 259° (decomp.) (Found: C, 71·7; H, 6·4. $C_{16}H_{17}ON_3$ requires C, 71·9; H, 6·4%).

1-*Ethyl*-7-*methylphenanthrene*.—Reaction of ethylmagnesium bromide on the preceding ketone followed by dehydration and dehydrogenation afforded 1-ethyl-7-methylphenanthrene, plates (from ethanol), m. p. 82·5° (Found: C, 92·8; H, 7·4. Calc. for $C_{17}H_{16}$: C, 92·7; H, 7·3%). The picrate forms long yellow needles, m. p. 117·5° (Found: C, 61·2; H, 4·3. Calc. for $C_{17}H_{16},C_6H_3O_7N_3$: C, 61·5; H, 4·2%) (cf. refs. 6 and 8).

Ethyl β-*Oxo*-α-(2-*o*-*tolylethyl*)*pimelate* (III; R′ = Me, R″ = H).—This *ester*, prepared under the standard conditions, had b. p. 195—198°/4 mm. (Found: C, 68·8; H, 8·1. $C_{20}H_{28}O_5$ requires C, 69·0; H, 8·0%). In sulphuric acid (20 ml.) it (10 g.) gave γ-(2-*carboxy*-5-*methyl*-3 : 4-*dihydro*-1-*naphthyl*)*butyric acid* (IV; R = R″ = H, R′ = Me), which on repeated crystallisation from aqueous acetic acid formed needles, m. p. 168° [Found: C, 69·9; H, 6·5%; equiv., 137·0. $C_{16}H_{18}O_4$ (dibasic) requires C, 70·0; H, 6·6%; equiv., 137·0] [*diethyl ester*, b. p. 200°/4 mm. (Found: C, 72·6; H, 7·9. $C_{20}H_{28}O_4$ requires C, 72·7; H, 7·9%)].

5 : 6 : 7 : 8 : 9 : 10-*Hexahydro*-1-*methyl*-8-*oxophenanthrene* (V; R′ = Me, R″ = R‴ = H).—The ester (IV; R = Et, R′ = Me, R″ = H) (5 g.) was heated with sodium (0·35 g.) in dry benzene (12 ml.), and the product hydrolysed. The *ketone* (2·1 g.), b. p. 175—180°/4 mm., formed plates, m. p. 94°, from light petroleum (b. p. 60—80°) (Found: C, 85·1; H, 7·6. $C_{15}H_{16}O$ requires C, 84·9; H, 7·5%). Its *semicarbazone* formed prisms (from ethanol), m. p. 260—262° (decomp.) (Found: C, 71·4; H, 7·1. $C_{16}H_{19}ON_3$ requires C, 71·4; H, 7·1%).

1-*Ethyl*-8-*methylphenanthrene*.—The above ketone (2·5 g.) was treated in boiling ether (30 ml.) for 3 hr. with excess of ethylmagnesium bromide. The product (2·5 g.) was dehydrated with formic acid and dehydrogenated. 1-Ethyl-8-methylphenanthrene (1·9 g.) formed plates (from ethanol), m. p. 106—107° (Found: C, 93·0; H, 7·3. Calc. for $C_{17}H_{16}$: C, 92·7; H, 7·3%). The picrate separated from ethanol in needles, m. p. 125° (Found: C, 61·3; H, 4·4. Calc. for $C_{17}H_{16},C_6H_3O_7N_3$: C, 61·5; H, 4·2%).

2-*Ethyl*-1 : 2 : 3 : 4 : 9 : 10-*hexahydro*-8-*methyl*-1-*oxophenanthrene* (V; R′ = Me, R″ = H, R‴ = Et).—The ester (IV; R = Et, R′ = Me, R″ = H) (6 g.) was treated with sodium (0·42 g.) and ethylated. The product (6 g.), hydrolysed in the usual way, gave a *ketone* (2·2 g.), b. p. 180°/3 mm., needles, m. p. 87—88° [from light petroleum (b. p. 40—60°)] (Found: C, 85·2; H, 8·3. $C_{17}H_{20}O$ requires C, 85·0; H, 8·3%). The *semicarbazone* separated from ethanol in prisms, m. p. 217—218° (Found: C, 72·4; H, 7·7. $C_{18}H_{23}ON_3$ requires C, 72·7; H, 7·7%).

2-*Ethyl*-1 : 8-*dimethylphenanthrene*.—A solution of the ketone (V; R′ = Me, R″ = H, R‴ = Et) (2 g.) in ether (25 ml.) was allowed to react with methylmagnesium iodide [from magnesium (0·8 g.), methyl iodide (2·4 ml.), and ether (30 ml.)]. The product (2 g.) was dehydrated to a hydrocarbon (1·9 g.), b. p. 160—165°/3 mm., which was dehydrogenated with

selenium (4 g.) at 300—320° for 30 hr. 2-Ethyl-1 : 8-dimethylphenanthrene (1·4 g.), b. p. 180—190°/3 mm., on two crystallisations from ethanol formed plates, m. p. 113° (Found : C, 92·1; H, 7·6. Calc. for $C_{18}H_{18}$: C, 92·3; H, 7·7%). The picrate formed orange-red needles (from ethanol), m. p. 148—149°. The trinitrobenzene derivative crystallised from ethanol in yellow needles, m. p. 167° (Found : C, 64·3; H, 4·7. Calc. for $C_{18}H_{18}.C_6H_3O_6N_3$: C, 64·4; H, 4·7%). King and King [10] give 113°, 148—149°, and 167° as the respective m. p.s.

γ-(2-Carboxy-5-methyl-1-naphthyl)butyric Acid (VI; R = R″ = H, R′ = Me).—The ethyl ester (IV; R = Et, R′ = Me, R″ = H) was dehydrogenated with sulphur and hydrolysed, giving this *acid*, prisms, m. p. 184—185° (from aqueous ethanol) [Found : C, 70·3; H, 5·7%; equiv., 136·2. $C_{16}H_{16}O_4$ (dibasic) requires C, 70·6; H, 5·8%; equiv., 136·0], whose *ethyl ester* had b. p. 200—202°/3 mm. (Found : C, 73·1; H, 7·5. $C_{20}H_{24}O_4$ requires C, 73·2; H, 7·3%).

1 : 2 : 3 : 4-*Tetrahydro-8-methyl-1-oxophenanthrene* (VII; R′ = Me, R″ = R‴ = H).—The ester (VI; R = Et, R′ = Me, R″ = H), on Dieckmann cyclisation and then hydrolysis, afforded this ketone,[13] plates, m. p. 165° [from light petroleum (b. p. 60—80°)] (Found : C, 85·7; H, 6·6. Calc. for $C_{15}H_{14}O$: C, 85·7; H, 6·7%). Haworth, Mavin, and Sheldrick [13] give m. p. 164—165°.

1-*Methyl*-8-*isopropylphenanthrene*.—The preceding ketone (3 g.) in benzene (35 ml.) was refluxed with *iso*propylmagnesium bromide [from magnesium (0·72 g.), *iso*propyl bromide (3·7 g.), and ether (30 ml.)] for 4 hr. The product on dehydration and then dehydrogenation yielded 1-methyl-8-*iso*propylphenanthrene, plates (from methanol), m. p. 100° (Found : C, 92·3; H, 7·7. Calc. for $C_{18}H_{18}$: C, 92·3; H, 7·7%). The picrate formed orange needles (from ethanol), m. p. 141° (Found : C, 61·7; H, 4·8. Calc. for $C_{18}H_{18}.C_6H_3O_7N_3$: C, 62·2; H, 4·5%). Short and Wang [11] give m. p. 101·5—102° and 142·5° respectively.

1 : 2 : 3 : 4-*Tetrahydro-8-methyl-1-oxo-2-isopropylphenanthrene* (VII; R′ = Me, R″ = H, R‴ = Pr^i).—The ester (VI; R = Et, R′ = Me, R″ = H) (4 g.) was allowed to react with powdered potassium (0·5 g.) in benzene, giving a solid potassio-derivative which was refluxed with *iso*propyl iodide (3 ml.) for 20 hr. and then hydrolysed in the usual way. The *ketone* (1·4 g.), b. p. 180°/3 mm., formed needles, m. p. 123—125°, from light petroleum (b. p. 60—80°) (Found : C, 85·4; H, 7·7. $C_{18}H_{20}O$ requires C, 85·7; H, 7·9%).

1-*Methyl*-7-*isopropylphenanthrene* (*Retene*).—The preceding ketone on Clemmensen reduction and then dehydrogenation gave 1-methyl-7-*iso*propylphenanthene,[8b, c] plates (from ethanol), m. p. 99° (Found : C, 92·1; H, 7·6. Calc. for $C_{18}H_{18}$: C, 92·3; H, 7·7%). The picrate, orange-yellow needles, m. p. 123—124°, was also prepared (Found : C, 62·1; H, 4·6. Calc. for $C_{18}H_{18}.C_6H_3O_7N_3$: C, 62·2; H, 4·5%).

1 : 2 : 3 : 4-*Tetrahydro-2 : 8-dimethyl-1-oxophenanthrene* (VII; R′ = R‴ = Me, R″ = H).—This [14] was prepared from the ester (VI; R = Et, R′ = Me, R″ = H), by sodium-condensation, methylation, and hydrolysis under the usual conditions. The ketone, b. p. 180°/4 mm., crystallised from light petroleum (b. p. 60—80°) as plates, m. p. 108—109° (Found : C, 86·0; H, 7·2. Calc. for $C_{16}H_{16}O$: C, 85·7; H, 7·1%), and gave a semicarbazone, prisms, m. p. 256—257° (decomp.) (Found : C, 72·3; H, 6·7. Calc. for $C_{17}H_{19}ON_3$: C, 72·6; H, 6·8%).

2 : 8-*Dimethyl*-1-*isopropylphenanthrene*.—The action of an excess of *iso*propylmagnesium bromide on the above ketone proceeded normally affording a product which on dehydration and then dehydrogenation gave 2 : 8-*dimethyl*-1-*isopropylphenanthrene*, flakes (from ethanol), m. p. 79° (Found : C, 91·5; H, 8·1. $C_{19}H_{20}$ requires C, 91·9; H, 8·1%). The *picrate* crystallises from ethanol in yellow needles, m. p. 130° (Found : C, 62·6; H, 4·9. $C_{19}H_{20}.C_6H_3O_7N_3$ requires C, 62·9; H, 4·8%).

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72. *Synthesis of Polycyclic Compounds. Part II.* The Ring Closure of β-Carboxy-γ-1-naphthylbutyric Acid.*

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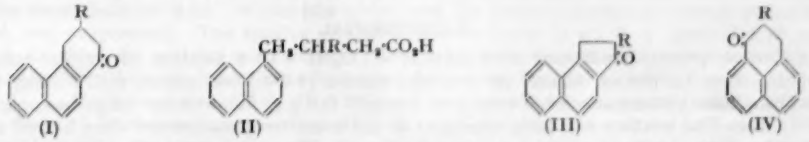
β-Carboxy-γ-1-naphthylbutyric acid, on ring closure with 85% sulphuric acid at 100°, affords 1 : 2 : 3 : 4-tetrahydro-1-oxophenanthrene-3-carboxylic acid as the sole product. The same substance is produced when the corresponding anhydride reacts with anhydrous aluminium chloride in nitrobenzene. The structure of the keto-acid has been confirmed by unambiguous synthesis.

In another investigation an appreciable quantity of 1 : 2 : 3 : 4-tetrahydro-1-oxophenanthrene-3-carboxylic acid (I; R = CO_2H) was required. Attwood, Stevenson, and Thorpe [1] showed that β-carboxy-γ-phenylbutyric acid in presence of concentrated sulphuric acid readily undergoes ring closure with the formation of 1 : 2 : 3 : 4-tetrahydro-4-oxonaphthalene-2-carboxylic acid. It seemed probable, therefore, that β-carboxy-γ-1-naphthylbutyric acid (II; R = CO_2H) should under similar conditions furnish the desired phenanthrene derivative (I; R = CO_2H).



Ethyl 1-naphthylmethylmalonate [2,3] was allowed to react with ethyl bromoacetate, and the resulting product on hydrolysis and decarboxylation afforded β-carboxy-γ-1-naphthylbutyric acid, which in 85% sulphuric acid at 100° readily cyclised to a ketonic acid.[4] This, by the above analogy,[5] should be represented as (I; R = CO_2H), although structures (III and IV; R = $CH_2{\cdot}CO_2H$) are also possible. However, it has been shown by Fieser and Gates [2] and by Ansell [6] that ring closure of a β-1-naphthylpropionic acid gives both a perinaphthan-1-one (IV; R = H) and a 4 : 5-benzindan-1-one (III; R = H). On the other hand, Ansell and Hey [7] demonstrated that an analogous cyclisation of α-1-naphthylmethylglutaric acid gives preferentially the 4 : 5-benzindanone (III; R = $CH_2{\cdot}CH_2{\cdot}CO_2H$).

To throw further light on this matter, we attempted to synthesise the isomeric keto-acids (I; R = CO_2H), (III; R = $CH_2{\cdot}CO_2H$), and (IV; R = $CH_2{\cdot}CO_2H$) by unequivocal methods.

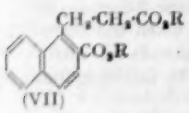
Methyl 2-oxo-1-phenethylbutane-1 : 4-dicarboxylate (V) (Bardhan, *J.*, 1936, 1851) was

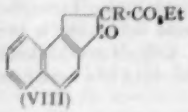
treated with cold concentrated sulphuric acid and the product on hydrolysis gave β-(2-carboxy-3 : 4-dihydro-1-naphthyl)propionic acid (VI; R = H). The corresponding ester (VI; R = Et) was dehydrogenated with sulphur and then hydrolysed, giving β-(2-carboxy-1-naphthyl)propionic acid (VII; R = H). The derived diethyl ester (VII; R = Et), on

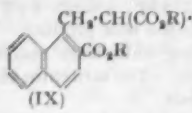
* Part I, preceding paper.

[1] Attwood, Stevenson, and Thorpe, *J.*, 1923, **123**, 1758.
[2] Fieser and Gates, *J. Amer. Chem. Soc.*, 1940, **62**, 2335.
[3] Darzens and Levy, *Compt. rend.*, 1935, **201**, 902; Mayer and Sieglitz, *Ber.*, 1922, **55**, 1835.
[4] Cf. Haworth, *J.*, 1932, 1129.
[5] Cf. Johnson, "Organic Reactions," Wiley, New York, 1944, Vol. II, Chap. 4, p. 116.
[6] Ansell, *J.*, 1954, 575.
[7] Ansell and Hey, *J.*, 1950, 2876.

Dieckmann cyclisation followed by treatment with ethyl bromoacetate, yielded ethyl (2-ethoxycarbonyl-1-oxo-4 : 5-benzindan-2-yl)acetate (VIII; R = $CH_2 \cdot CO_2Et$); hydrolysis with a mixture of concentrated hydrochloric acid and acetic acid then furnished 1-oxo-3 : 4-benzindan-2-ylacetic acid (III; R = $CH_2 \cdot CO_2H$), which did not give a semicarbazone under the usual conditions. On the other hand, alkaline hydrolysis of the ester (VIII; R = $CH_2 \cdot CO_2Et$) furnished β-carboxy-γ-(2-carboxy-1-naphthyl)butyric acid (IX;


(VII)


(VIII)


(IX)

R = H), the triester of which, by the Dieckmann procedure, gave 1 : 2 : 3 : 4-tetrahydro-1-oxo-phenanthrene-3-carboxylic acid (I; R = CO_2H), identical with the previous product the structure of which is therefore established.

The keto-acid (IV; R = $CH_2 \cdot CO_2H$) could not be obtained from 8-formyl-1-naphthoic acid,[8] nor as yet by other methods.

Several new 4 : 5-benzindan-1-ones have also been prepared.

Experimental

β-Carboxy-γ-1-naphthylbutyric Acid (II; R = CO_2H).—To a solution of sodium ethoxide prepared from anhydrous ethanol (60 ml.) and sodium (3·5 g.) was added, with cooling, ethyl 1-naphthylmethylmalonate (cf. Fieser and Gates[2]) (45 g.), followed by ethyl bromoacetate (16·8 ml.). The mixture was kept overnight at the room temperature and then heated under reflux for 7 hr. After cooling, potassium hydroxide (42 g.) in water (20 ml.) and ethanol (65 ml.) were added and the whole again boiled for 1 hr. The excess of ethanol was removed on the steam-bath, and the solution cooled in ice and acidified with 2N-hydrochloric acid. The oily precipitate solidified and was decarboxylated at 180—190° for 2 hr. The resulting acid was dissolved in aqueous sodium carbonate, the solution was filtered and acidified, and the solid precipitate collected. On purification from acetic acid (charcoal) *β-carboxy-γ-1-naphthylbutyric acid* formed prisms, m. p. 183° (Found : C, 69·9; H, 5·5. $C_{15}H_{14}O_4$ requires C, 69·7; H, 5·4%). The *anhydride* (5 g.), prepared by heating the acid (8 g.) with acetic anhydride (24 ml.) for 4 hr., had b. p. 220°/4 mm.; it solidified and recrystallised from light petroleum (b. p. 60—80°), in which it is sparingly soluble, as plates, m. p. 135—136° (Found : C, 74·9; H, 5·1. $C_{15}H_{12}O_3$ requires C, 75·0; H, 5·0%). The *anilic acid*, obtained on mixing the anhydride with aniline in dry benzene, crystallised from ethanol as prisms, m. p. 197° (Found : C, 75·5; H, 5·7. $C_{21}H_{19}O_3N$ requires C, 75·7; H, 5·7%), and when heated at 207° for 0·5 hr. gave the *anil*, needles (from ethanol), m. p. 138° (Found : C, 79·6; H, 5·5. $C_{21}H_{17}O_2N$ requires C, 80·0; H, 5·4%).

1 : 2 : 3 : 4-*Tetrahydro-1-oxophenanthrene-3-carboxylic Acid* (I; R = CO_2H).—(*a*) β-Carboxy-γ-1-naphthylbutyric acid (2 g.) was heated on the water-bath with concentrated sulphuric acid (6 ml.) and water (2 ml.) for 1·5 hr. The solution was cooled and poured on ice, and the solid collected. Repeated crystallisation from ethanol (charcoal) gave 1 : 2 : 3 : 4-*tetrahydro-1-oxophenanthrene-3-carboxylic acid* as plates, m. p. 218° (Found : C, 74·9; H, 5·1. $C_{15}H_{12}O_3$ requires C, 75·0; H, 5·0%). The *semicarbazone* crystallised from aqueous acetic acid in scales, m. p. 268° (decomp.) (Found : C, 64·3; H, 5·1. $C_{16}H_{15}O_3N_3$ requires C, 64·6; H, 5·0%).

(*b*) The anhydride of β-carboxy-γ-1-naphthylbutyric acid (5 g.), dissolved in nitrobenzene (35 ml.), was added gradually with stirring to a solution of anhydrous aluminium chloride (6 g.) in nitrobenzene (25 ml.) cooled in ice. After 2 days at room temperature the mixture was decomposed with ice and dilute hydrochloric acid, and the excess of nitrobenzene distilled off in steam. The solid residue on purification from ethanol gave the 3-carboxylic acid, m. p. 218°, identical with that prepared by method (*a*). The *ethyl ester* was prepared by heating the acid (10 g.) with ethanol (40 ml.), and 4 ml. of ethanol previously saturated with hydrogen chloride at 0°, for 10 hr., forming a pale yellow liquid (8·4 g.), b. p. 210—214°/4 mm., colourless needles, m. p. 99—100° (from aqueous ethanol) (Found : C, 76·0; H, 6·0. $C_{17}H_{16}O_3$ requires C, 76·1; H, 5·9%).

[8] Cf. Graebe and Gfeller, *Annalen*, 1893, **276**, 13.

β-(2-*Carboxy*-3 : 4-*dihydro*-1-*naphthyl*)*propionic Acid* (VI; R = H).—Methyl 2-oxo-1-phenethylbutane-1 : 4-dicarboxylate[9] (5 g.) was stirred during 3 hr. with sulphuric acid (*d* 1·84; 30 ml.) at −10°. The product was poured on ice, the organic layer collected in ether, and the solvent removed from the dried extract. The residue was hydrolysed with potassium hydroxide (2·5 g.) in water (2 ml.) and ethanol (25 ml.) in the usual way, yielding β-(2-*carboxy*-3 : 4-*dihydro*-1-*naphthyl*)*propionic acid* (3 g.) which on repeated crystallisation from aqueous acetic acid (charcoal) formed colourless prisms, m. p. 171° (Found : C, 68·4; H, 5·6. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7%). The *ethyl ester* had b. p. 194—195°/3 mm. (Found : C, 70·9; H, 7·1. $C_{18}H_{22}O_4$ requires C, 71·5; H, 7·3%).

β-(2-*Carboxy*-1-*naphthyl*)*propionic Acid* (VII; R = H).—The preceding ester (10 g.) was heated with sulphur (1·07 g.) at 240—250° for 2 hr. On distillation, a liquid (8·5 g.), b. p. 195—205°/4 mm., was collected, which on hydrolysis by boiling 20% ethanolic potassium hydroxide (50 ml.) for 1 hr. gave β-(2-*carboxy*-1-*naphthyl*)*propionic acid*, needles (from aqueous ethanol; charcoal), m. p. 203° (Found : C, 68·9; H, 5·0. $C_{14}H_{12}O_4$ requires C, 68·8; H, 4·9%). The *ethyl ester*, prepared by means of ethanol and sulphuric acid, had b. p. 196—198°/3 mm. (Found : C, 71·8; H, 6·7. $C_{16}H_{20}O_4$ requires C, 72·0; H, 6·7%).

Ethyl 2-*Ethoxycarbonyl*-1-*oxo*-4 : 5-*benzindan*-2-*ylacetate* (VIII; R = CH_2CO_2Et).—The foregoing ester (6 g.), dry benzene (25 ml.), and sodium (0·46 g.) were heated under reflux until formation of the biscuit-coloured sodio-derivative was complete (2 hr.), then cooled in ice and treated with ethyl bromoacetate (2·5 ml.), kept at room temperature overnight, and then heated on the steam-bath for 6 hr. Water was added, and the benzene layer was washed with water, dried, and evaporated. The residue yielded a viscous liquid (5 g.), b. p. 210—215°/3 mm., which solidified on rubbing with ethanol. On recrystallisation from aqueous ethanol *ethyl* 2-*ethoxycarbonyl*-1-*oxo*-4 : 5-*benzindan*-2-*ylacetate* formed needles, m. p. 103° (Found : C, 70·5; H, 5·8. $C_{20}H_{20}O_5$ requires C, 70·6; H, 5·8%), not giving a colour with ethanolic ferric chloride.

1-*Oxo*-4 : 5-*benzindan*-2-*ylacetic Acid* (III; R = $CH_2{\cdot}CO_2H$).—The above keto-ester (VIII; R = $CH_2{\cdot}CO_2Et$) (2 g.) was boiled with concentrated hydrochloric acid (5 ml.) and acetic acid (10 ml.) for 10 hr. 1-*Oxo*-4 : 5-*benzindan*-2-*ylacetic acid* separated from ethanol in needles, m. p. 226—227° (Found : C, 74·9; H, 5·1%; equiv., 240·2. $C_{14}H_{11}O{\cdot}CO_2H$ requires C, 75·0; H, 5·0%; equiv., 240·0).

β-*Carboxy*-γ-(2-*carboxy*-1-*naphthyl*)*butyric Acid* (IX; R = H).—The keto-ester (VIII; R = $CH_2{\cdot}CO_2Et$) (5 g.) was boiled with potassium hydroxide (5 g.) in water (3 ml.) and ethanol (10 ml.) for 1 hr. The excess of ethanol was evaporated, and the residual solution extracted once with ether and acidified with hydrochloric acid. The *butyric acid* separated from hot water (charcoal) in nodules, m. p. 214—215° [Found : C, 63·4; H, 4·6%; equiv., 101·0. $C_{12}H_{11}(CO_2H)_3$ requires C, 63·6; H, 4·6%; equiv., 100·7]. The *triethyl ester* was prepared by heating the acid (6 g.) with ethanol (35 ml.) and concentrated sulphuric acid (3·5 ml.) at 115—120° in a current of ethanol vapour for 6 hr. It (5·4 g.) had b. p. 215—217°/3 mm. (Found : C, 68·3; H, 6·7. $C_{22}H_{28}O_6$ requires C, 68·4; H, 6·7%).

Tetrahydro-1-*oxophenanthrene*-3-*carboxylic Acid* (I; R = CO_2H) (cf. above).—(*c*) The above ester (5 g.) was heated on the steam-bath with powdered sodium (0·31 g.) and dry benzene (12 ml.) for 2 hr. On cooling, ice and hydrochloric acid were added and the benzene layer was washed with water, dried, and evaporated. The residue (5 g.) was hydrolysed by hot concentrated hydrochloric acid (10 ml.) and acetic acid (20 ml.) for 12 hr. On repeated crystallisation from ethanol (charcoal) the phenanthrene acid formed plates, m. p. and mixed m. p. 218—219° (Found : C, 74·9; H, 5·0. Calc. for $C_{15}H_{12}O_3$: C, 75·0; H, 5·0%). The semicarbazone separated from acetic acid in prisms, m. p. and mixed m. p. 268° (decomp.) (Found : C, 64·5; H, 5·1. Calc. for $C_{16}H_{15}O_3N_3$: C, 64·6; H, 5·0%).

6 : 7 : 8 : 9-*Tetrahydro*-4 : 5-*benzindan*-1-*one*.—β-(2-Carboxy-3 : 4-dihydro-1-naphthyl)propionic acid (5 g.), on reduction with sodium amalgam (200 g.; 3%) in the usual way, gave the *tetrahydro-acid* as a semisolid mass (5 g.) which was boiled with acetic anhydride (15 ml.) for 3 hr. and then slowly distilled. The *ketone* (3 g.) thus obtained had b. p. 140°/3 mm. (Found : C, 83·7; H, 7·6. $C_{13}H_{14}O$ requires C, 83·9; H, 7·5%). The *semicarbazone* had m. p. 235° (Found : 69·1; H, 7·0. $C_{14}H_{17}ON_3$ requires C, 69·1; H, 7·0%). A mixture of the ketone (5 g.) and ethyl formate (10 ml.) was gradually introduced into powdered sodium (5 g.) kept under anhydrous benzene (150 ml.) at 0°. The whole was kept in ice overnight, then diluted with ice-water, and the aqueous solution was separated and acidified. The crystalline *hydroxymethylene derivative* which separated was collected, washed with water, and on recrystallisation from aqueous acetone had m. p. 149—150° (Found : C, 78·4; H, 6·5. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·5%).

6 : 7-*Dihydro*-4 : 5-*benzindan*-1-*one*.—β-(2-Carboxy-3 : 4-dihydro-1-naphthyl)propionic acid, on treatment with acetic anhydride in the usual way, readily afforded **6 : 7-*dihydro*-4 : 5-*benzindan*-1-*one***, prisms, m. p. **86°**, from light petroleum (b. p. 40—60°) (Found : C, **84·7**; H, 6·5. $C_{13}H_{12}O$ requires C, **84·8**; H, 6·5%).

4 : 5-*Benzindan*-1-*one* (III; R = H).—β-(2-Carboxy-1-naphthyl)propionic acid, on treatment with acetic anhydride, gave an oil, b. p. **160—165°/3** mm., which solidified and on further purification from light petroleum (b. p. **60—80°**) afforded needles, m. p. **126—127°** (Found : C, 85·7; H, 5·4. Calc. for $C_{13}H_{10}O$: C, 85·7; H, 5·5%). Fieser and Gates (*loc. cit.*) record m. p. 120·6—121·4°; Cook and Hewett (*J.*, **1934**, 373) give m. p. 120—121°.

4-Oxo-7-phenylheptanoic Acid.—Methyl 2-oxo-1-phenethylbutane-1 : 4-dicarboxylate [9] (V) on hydrolysis with concentrated hydrochloric acid and acetic acid yielded the ***keto-acid***, which on recrystallisation from light petroleum (b. p. **40—60°**) formed needles, m. p. **83°** (Found : C, 70·8; H, 7·3. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%). The *semicarbazone* separated from ethanol (charcoal) in prisms, m. p. **168—169°** (Found : C, 60·4; H, 6·9. $C_{14}H_{19}O_3N_3$ requires C, 60·6; H, 6·9%).

5-Methyl-4-oxo-7-phenylheptanoic acid, prepared from methyl 1-methyl 2-oxo-1-phenethylbutane-1 : 4-dicarboxylate [9] in an analogous manner, crystallised from light petroleum (b. p. 40—60°) as needles, m. p. **73—74°** (Found : C, 71·9; H, 7·7. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). This did not, however, give a semicarbazone under the usual conditions.

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[9] Bardhan and Nasipuri, preceding paper.

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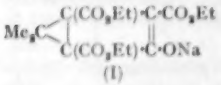
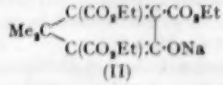
73. *Terpene Compounds. Part IX.* A Method of Formation of Homoapocamphoric Acid.*

By R. N. ADHYA, A. C. GHOSH, and J. C. BARDHAN.

The product of the action of ethyl bromoacetate on Perkin and Thorpe's yellow sodium compound from ethyl αα′-dibromo-ββ-dimethylglutarate and ethyl sodiomalonate [1] on successive hydrogenation, hydrolysis, and Wolff–Kishner reduction affords homo*apo*camphoric acid, the formation of which is consistent only with the monocyclic structure (II) for the yellow compound. An authentic specimen of homo*apo*camphoric acid has been prepared by the condensation of ethyl 2 : 2-dimethyl-3-oxo*cyclo*pentanecarboxylate [2] with ethyl cyanoacetate followed by catalytic reduction and hydrolysis. A new preparation of *cis-apo*camphoric acid *via* the cyanohydrin of ethyl 2 : 2-dimethyl-3-oxo*cyclo*pentanecarboxylate is also described.

THE yellow sodium compound, $C_{16}H_{21}O_7Na$, first prepared by Perkin and Thorpe [1] from ethyl αα′-dibromo-ββ-dimethylglutarate, ethyl sodiomalonate, and sodium ethoxide has formed the subject of much controversy. As a result of many investigations Perkin, Thorpe, and their co-workers [3] were led to represent it as (I). According to Toivonen,[4]


(I)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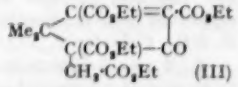
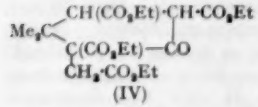

(III)

on the other hand, the sodio-derivative consists largely, at any rate, of the unsaturated monocyclic structure (II). The present communication records certain observations which support the latter view. Thus it is found that the compound readily condenses with

* Part VIII, *J.*, 1956, 260.

[1] Perkin and Thorpe, *J.*, 1901, **79**, 729.
[2] *Idem*, *J.*, 1904, **85**, 18.
[3] Cf. Farmer and Ingold, *J.*, 1920, **117**, 1362; Farmer, Ingold, and Thorpe, *J.*, 1922, **121**, 128; and later papers.
[4] Toivonen, *Ann. Acad. Sci. Fennicæ*, 1927, **19**, 20; *Annalen*, 1919, **419**, 176; *Acta Sci. Fennicæ, Phys.-math., Cl.* I, 1922, **26**, 1.

ethyl bromoacetate, giving ethyl 1 : 2 : 4-triethoxycarbonyl-2 : 2-dimethyl-5-oxo*cyclo*pent-3-enylacetate (III), which is hydrogenated over Adams's catalyst at room temperature to the saturated ester (IV); the bridged-ring analogue would not be expected to react under such mild conditions.[5] On hydrolysis with hydrochloric acid the latter afforded 3-carboxy-2 : 2-dimethyl-5-oxo*cyclo*pentylacetic acid (V), yielding on Wolff–Kishner reduction 3-carboxy-2 : 2-dimethyl*cyclo*pentylacetic acid (homo*apo*camphoric acid[6]) (VI), the identity of which was established by comparison with a specimen prepared as follows.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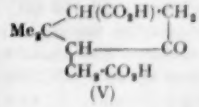
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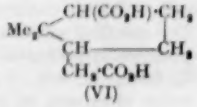
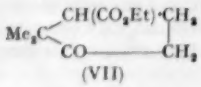
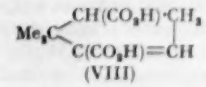
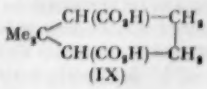

(VI)

Ethyl 2 : 2-dimethyl-3-oxo*cyclo*pentanecarboxylate[7] (VII), prepared by an improved method, was allowed to react with hydrogen cyanide; the product on dehydration with phosphorus oxychloride and pyridine followed by hydrolysis with hydrochloric acid gave a good yield of 2 : 2-dimethyl*cyclo*pent-3-ene-1 : 3-dicarboxylic acid (VIII), which on


(VII)

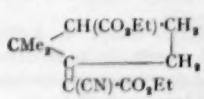

(VIII)

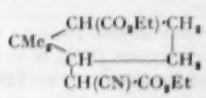

(IX)

hydrogenation in acetic acid in presence of Adams's catalyst gave *cis-apo*camphoric acid[8] (IX). The corresponding anhydride, however, could not be converted satisfactorily into homo*apo*camphoric acid by Komppa's method.[6]

The keto-ester (VII) readily condensed with ethyl cyanoacetate under the conditions

(X)




(XI)

prescribed by Cope *et al.*,[9] giving the cyano-ester (X), which on hydrogenation in alcohol in presence of palladised charcoal[10] afforded the saturated ester (XI). This was hydrolysed by hydrochloric acid to homo*apo*camphoric acid (VI), identical with the product obtained from Perkin and Thorpe's compound. The bicyclic structure (I) for the latter is thus untenable.[11]

Experimental

The crude sodium compound prepared according to Perkin and Thorpe's directions[1] was recrystallised once from boiling absolute ethanol.

Ethyl 1 : 3 : 4-*Triethoxycarbonyl*-2 : 2-*dimethyl*-5-*oxo*cyclo*pent*-3-*enylacetate* (III).—The preceding sodium compound (15 g.) was suspended in dry benzene (50 ml.), ethyl bromoacetate (6 ml.) was added, and the mixture refluxed until the original deep yellow colour had almost disappeared (40—45 hr.). The mixture was diluted with water, the benzene layer isolated, and the aqueous solution extracted with benzene. The benzene extract was washed with dilute sodium carbonate solution and water, dried, and distilled. The *product* (14·5 g.) had b. p. 195—196°/4 mm., $d_4^{21\cdot5}$ 1·1530, $n_D^{21\cdot5}$ 1·4804, $[R_L]_D$ 101·6 (Calc., 98·52) (Found: C, 57·6; H, 6·7. $C_{20}H_{28}O_9$ requires C, 58·2; H, 6·7%). It gives no colour with ethanolic ferric chloride.

Ethyl 1 : 3 : 4-*Triethoxycarbonyl*-2 : 2-*dimethyl*-5-*oxo*cyclo*pentylacetate* (IV).—The preceding ester (39 g.) in ethanol (30 ml.) was shaken with Adams's catalyst (0·3 g.) in hydrogen at 30°

[5] Cf. Shriner and Adams, *J. Amer. Chem. Soc.*, 1925, **47**, 2733.
[6] Cf. Komppa, *Ber.*, 1911, **44**, 1541.
[7] (*a*) Perkin and Thorpe, *J.*, 1904, **85**, 18; (*b*) Gibson, Hariharan, and Simonsen, *J.*, 1927, 3009.
[8] (*a*) Marsh and Gardner, *J.*, 1896, **69**, 64; (*b*) Wallach, *Annalen*, 1898, **300**, 317; 1901, **315**, 291; (*c*) Gardner and Cockburn, *J.*, 1898, **73**, 278.
[9] Cope, Hofmann, Wyckoff, and Hardenbergh, *J. Amer. Chem. Soc.*, 1941, **63**, 3452.
[10] Hartung, *ibid.*, 1928, **50**, 3372.
[11] Cf. Acheson and Robinson, *J.*, 1952, 1130.

(absorption, 2436 ml. in 3·5 hr.; calc., 2441 ml.). The solution was filtered, excess of ethanol evaporated off, and the residue distilled, giving the saturated *ester* (36·6 g.), b. p. 190—191°/4 mm., which crystallised and recrystallised from light petroleum (b. p. 40—60°) as needles (18 g.), m. p. 75—76° (Found: C, 57·8; H, 7·2. $C_{20}H_{36}O_9$ requires C, 57·9; H, 7·2%). It gives a violet colour with ferric chloride. The mother-liquor was evaporated and the residue on distillation gave an oil, b. p. 185—188°/3 mm. This partly solidified and also showed a positive ferric reaction.

3-*Carboxy*-2 : 2-*dimethyl*-5-*oxo*cyclo*pentylacetic Acid* (V).—The foregoing keto-ester (9 g.) was refluxed with concentrated hydrochloric acid (50 ml.) until a clear solution resulted (20 hr.). The solution was evaporated to dryness on the steam-bath and the crystalline product (4·2 g.) purified by recrystallisation from water. The *diacid* formed prisms, m. p. 183—184° (Found: C, 56·0; H, 6·6. $C_{10}H_{14}O_5$ requires C, 56·1; H, 6·5%). The *semicarbazone* separated from water in prisms, m. p. 228° (decomp.) (Found: C, 48·3; H, 6·2. $C_{11}H_{17}O_5N_3$ requires C, 48·7; H, 6·3%). The *ethyl ester*, prepared with ethanolic hydrogen chloride, had b. p. 155°/4 mm. (Found: C, 62·0; H, 8·1. $C_{14}H_{22}O_5$ requires C, 62·2; H, 8·2%).

3-*Carboxy*-2 : 2-*dimethyl*cyclo*pentylacetic* (*Homoapocamphoric*) *Acid* (VI).—(*a*) The semicarbazone (1 g.) described above was heated with a solution from sodium (1·2 g.) in absolute ethanol (6 ml.) at 180—190° for 26 hr. On cooling, water was added, the excess of ethanol removed on the water-bath, the solution acidified with hydrochloric acid, and the solid collected. Recrystallisation from water (charcoal) gave prisms, m. p. 202—203° (Komppa [6] gives m. p. 203—204°) (Found: C, 59·8; H, 8·0. Calc. for $C_{10}H_{16}O_4$: C, 60·0; H, 8·0%). This showed no m. p. depression with homo*apo*camphoric acid described below.

(*b*) The keto-ester (V) (4·5 g.), amalgamated zinc (50 g.), and concentrated hydrochloric acid (50 ml.) were refluxed for 30 hr., during which concentrated hydrochloric acid (5 × 10 ml.) was added. The solution was evaporated to a small bulk, saturated with ammonium sulphate, and extracted repeatedly with ether. The ethereal solution was washed with a little water, dried, and evaporated. The residue on recrystallisation from water gave homo*apo*camphoric acid, m. p. 201—202°.

2 : 2-*Dimethyl*cyclo*pent*-3-*ene*-1 : 3-*dicarboxylic Acid* (VIII).—Ethyl 2 : 2-dimethyl-3-oxo-*cyclo*pentanecarboxylate (VII), b. p. 95°/3 mm., was prepared essentially as described by Perkin and Thorpe and by Gibson *et al.*,[7] but the following modification was more satisfactory for the preparation of large quantities of 4-methylpentane-1 : 3 : 4-tricarboxylic acid. Ethyl αβ-dicyano-β-methylbutyrate,[12] b. p. 129—131°/6 mm., was prepared by the addition of hydrogen cyanide to ethyl 2-cyano-3-methylbut-2-enoate [13] as described by Hope and Sheldon [14] in an analogous case. A stirred solution of ethyl αβ-dicyano-β-methylbutyrate (18 g.) in *tert.*-butyl alcohol (40 ml.), heated to 40°, was mixed with methanolic 30% potassium hydroxide (1 ml.), then treated dropwise with acrylonitrile (6 g.) in *tert.*-butyl alcohol (20 ml.) during 30 min. The mixture was heated at 40—45° for a further 2 hr., diluted with water (100 ml.), and acidified with 10% hydrochloric acid (40 ml.), and the oil was collected in benzene. The benzene solution was washed with water, dried, and distilled. The resulting *ethyl* 2 : 3 : 5-*tricyano*-2-*methylpentane*-3-*carboxylate* (18 g.) had b. p. 185—190°/8 mm. (Found: C, 61·6; H, 6·6. $C_{13}H_{15}O_2N_3$ requires C, 61·8; H, 6·4%). This on hydrolysis with sulphuric acid [7b] readily yielded 4-methylpentane-1 : 3 : 4-tricarboxylic acid, m. p. 155°.

Hydrogen cyanide (from potassium cyanide, 10 g.), cooled in a freezing mixture, was treated with a few drops of potassium cyanide solution and then dropwise with ethyl 2 : 2-dimethyl-3-oxo*cyclo*pentanecarboxylate (5 g.). The mixture was kept in ice over-night, then treated with two drops of concentrated sulphuric acid, the excess of hydrogen cyanide was removed, and the product heated at 140—150° with pyridine (85 ml.) and phosphorus oxychloride (23 ml.) for 1 hr. On cooling, ice-water was added and the solution acidified with concentrated hydrochloric acid (40 ml.) and extracted with ether. The ethereal solution was washed, dried, and evaporated, and the residual oil refluxed with concentrated hydrochloric acid (70 ml.) for 20 hr. 2 : 2-*Dimethyl*cyclo*pent*-3-*ene*-1 : 3-*dicarboxylic acid* (4·3 g.) which separated on cooling recrystallised from water in needles, m. p. 212° (Found: C, 58·8; H, 6·7. $C_9H_{12}O_4$ requires C, 58·7; H, 6·5%).

cis-apo*Camphoric Acid* (IX).—The foregoing unsaturated acid (2 g.), dissolved in purified acetic acid (30 ml.), was shaken with Adams's catalyst (0·1 g.) in hydrogen at 23°; the calculated

[12] Higson and Thorpe, *J.*, 1906, **89**, 1465.
[13] Vogel, *J.*, 1928, 2019.
[14] Hope and Sheldon, *J.*, 1922, **121**, 2223.

quantity of hydrogen was absorbed in 15 min. The solution was filtered and evaporated, and the solid residue recrystallised from water, giving needles, m. p. 205—206° (Found : C, 58·2; H, 7·6. Calc. for $C_9H_{14}O_4$: C, 58·1; H, 7·5%). Marsh and Gardner [8a] record m. p. 203—204°; Wallach [8b] gives m. p. 205—206°; and Komppa [15] gives m. p. 203·5—204·5°. The anhydride prepared by the action of acetyl chloride crystallised from chloroform–light petroleum (b. p. 40—60°) as needles, m. p. 177° (Komppa [15] gives m. p. 174·5—175·5°; Wallach [8b] gives m. p. 176—177°) (Found : C, 64·0; H, 6·9. Calc. for $C_9H_{12}O_3$: C, 64·3; H, 7·1%).

Ethyl α-Cyano-α-(3-ethoxycarbonyl-2 : 2-dimethylcyclopentylidene)acetate (X).—Ethyl 2 : 2-dimethyl-3-oxocyclopentanecarboxylate (VII) (11·4 g.), ethyl cyanoacetate (7 ml.), acetic acid (10 ml.), ammonium acetate (3·8 g.), and benzene (50 ml.) were heated at 150—160° for 3 hr. The benzene layer was isolated, washed with a little water, dried, and distilled, giving the cyclopentylideneacetate (11·3 g.), b. p. 200—202°/12 mm. (Found : C, 64·2; H, 7·5. $C_{15}H_{21}O_4N$ requires C, 64·5; H, 7·5%).

Ethyl α-Cyano-α-(3-ethoxycarbonyl-2 : 2-dimethylcyclopentyl)acetate (XI).—A solution of the unsaturated ester (X) (10·2 g.) in ethanol (10 ml.) was shaken with palladised charcoal (1 g.) in hydrogen at 24° until 943 ml. of hydrogen (943 ml.) had been absorbed. The solution was filtered, the solvent removed, and the residue distilled, giving the cyclopentylacetate (9·3 g.), b. p. 195—197°/12 mm. (Found : C, 63·9; H, 8·2. $C_{15}H_{23}O_4N$ requires C, 64·0; H, 8·2%).

Homoapocamphoric Acid.—The foregoing ester (10·3 g.) was heated with concentrated hydrochloric acid (100 ml.) for 6 hr. The acid (3 g.) which separated on cooling was collected and on repeated crystallisation from water formed prisms, m. p. 202—203° alone or on admixture with the acid described above (Found : C, 59·9; H, 8·0. Calc. for $C_{10}H_{16}O_4$: C, 60·0; H, 8·0%).

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[15] Komppa, *Ber.*, 1901, **34**, 2474; *Annalen*, 1909, **368**, 126.

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74. *Anhydro-compounds from Nitrogen-containing Derivatives of Thioglycollic Acid. Part II.* Glyoxaline and Benziminazole Compounds.*

By G. F. DUFFIN and J. D. KENDALL.

(2-Benziminazolylthio)acetic acid (I; R = R′ = X = H) with acetic anhydride gives a thiazolidone (II) from which *mero*cyanine dyes have been prepared. 1-Substituted acids (I; R′ = X = H), like the corresponding quinoline compounds (Part I *), give stable anhydro-compounds which may be represented as (III) but which, unlike the quinoline anhydro-compounds, usually give products derived by attack of the reagent at two different points in the molecule. No anhydro-compounds corresponding to those derived from (2-quinolylthio)-propionic and -butyric acid could be obtained from the acids (I; R = Me or Et).

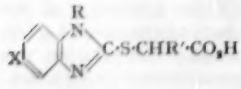
As mentioned in Part I,* dehydration of (2-benziminazolylthio)acetic acid (I; R = R′ = X = H) gives the thiazolidone (II) which possesses a very reactive methylene group (Kendall and Duffin, B.P. 634,951—2). Compounds of type (I; R = Me or Ph, X = H or NO_2), which may be prepared from the appropriate α-halogeno-acid and a 1-substituted benziminazole-2-thiol (V; R = Me or Ph, X = H or NO_2, Y = SH) by the methods of Everett [1] or Stephen and Wilson,[2] cannot undergo dehydration to a thiazolidone, but those in which R = H, like the corresponding (2-quinolylthio)acetic acids (Parts I), give anhydro-compounds of analogous structures (III). [Added, 19.9.55 : After this paper had been submitted, publications appeared from Wilson Baker and Ollis [3] and Bieber [4] in

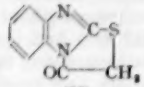
* Part I, *J.*, 1951, 734.

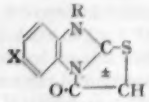
[1] Everett, *J.*, 1931, 3042.
[2] Stephen and Wilson, *J.*, 1928, 1420.
[3] Baker and Ollis, *Chem. and Ind.*, 1955, 910.
[4] Bieber, *ibid.*, p. 1055.

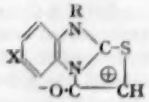
which new formulations were proposed for mesoionic structures. In accordance with that of the former, the compounds formulated as (III) would be represented by (*A*). The present authors cannot see how this helps to explain the reactions of their compounds, and it ignores the special character of intracyclic sulphur atoms which, as will be shown in later papers, have a decided effect on the properties of ring systems.]

That the acids (I) have the structure assigned to them and not that of the isomeric compounds (IV; R = Me or Ph, Z = $CHR'\cdot CO_2H$) is shown by the similarity of their ultraviolet absorptions in ethanol to that of the parent (I; R = R′ = X = H) and 1-methyl-2-methylthiobenziminazole (V; R = Me, X = H, Y = SMe) with maxima at 2850 and 2920 Å, and dissimilarity from that of 2 : 3-dihydro-1 : 3-dimethyl-2-thiobenziminazole (IV; R = Z = Me) which has a simple maximum at 3120 Å.

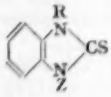

(I)

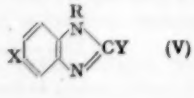

(II)


(III)

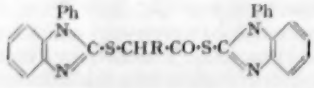

(*A*)

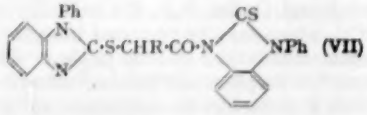
Like the corresponding quinoline derivatives the compounds (III) are stable, high-melting, and sparingly soluble in most organic solvents. Molecular-weight determinations were possible only on the anhydro-compound (III; R = Ph, X = H) and these indicated that the compound was unimolecular in camphor but was associated in acetic acid.

(IV) 


(V)

The anhydro-compounds obtained from (I; R = Ph or Me, R′ = X = H) were studied in detail. Although stable to boiling water, the anhydro-compound (III; R = Ph, X = H) was rapidly reduced by zinc dust and ethanolic hydrochloric acid to the thiol (V; R = Ph, X = H, Y = SH). With ethanolic sulphuric acid, the compound (III; R = Ph, X = H) gave mainly an oil which could not be purified, together with some of the thiol (V; R = Ph, X = H, Y = SH). The oil reacted rapidly with aqueous alkali to give ethanol and the acid (I; R = Ph, R′ = H, X = H) and was presumed to be the ester (V; R = Ph, X = H, Y = $S\cdot CH_2\cdot CO_2Et$). Attempts to prepare the pure ester by unequivocal methods were, however, unsuccessful. With 50% aqueous sulphuric or hydrochloric acid, the anhydro-compound gave mainly the parent acid and a compound $C_{28}H_{20}ON_4S_2$. The latter was stable to acid but was hydrolysed by aqueous alkali to the thiol and the parent acid, which suggested that it had structure (VI or VII; R = H). With acetic anhydride it gave the 3-acetyl-2-thione (IV; R = Ph, Z = Ac) which had the

(VI) 


(VII)

characteristic ultraviolet absorption in ethanol of a benziminazole-2-thione. The absorption of the compound $C_{28}H_{20}ON_4S_2$, however, included only the two maxima which are characteristic of the benziminazole ring and no maximum at 3120 Å, indicating that the compound had structure (VI; R = H).

With hot dilute nitric acid the anhydro-compound was rapidly oxidised to a mixture of 1-phenylbenziminazole (V; R = Ph, X = Y = H) and its 2-hydroxy-5-nitro-derivative

(V; R = Ph, X = NO_2, Y = OH), the latter being similarly obtained from the 5-nitro-anhydro-compound (III; R = Ph, X = NO_2). Under similar conditions the parent acid was unaffected whilst 2-hydroxy-1-phenylbenziminazole (V; R = Ph, X = H, Y = OH) gave the nitro-compound in high yield and 1-phenylbenziminazole-2-thiol gave 1-phenylbenziminazole only. It is suggested therefore that the compounds (V; R = Ph, X = H, Y = OH and SH) are the primary products of the action of dilute nitric acid on the anhydro-compound.

Aqueous-ethanolic sodium hydroxide or carbonate reacted with the anhydro-compound, giving equimolar proportions of 2-hydroxy-1-phenylbenziminazole and 1-phenylbenziminazole-2-thiol, which recrystallised as a eutectic.

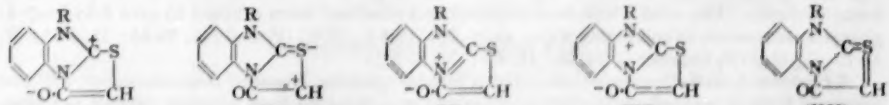
With excess of boiling benzylamine, the anhydro-compound gave the thiol and 2-benzylamino-1-phenylbenziminazole (V; R = Ph, X = H, Y = $NH{\cdot}CH_2Ph$), the latter also being obtained in high yield, under similar conditions, from the parent acid.

Corresponding products were obtained from the anhydro-compound (III; R = Me, X = H) by similar reactions, except that hydrolysis with aqueous sulphuric acid gave *only* the parent acid (I; R = Me, R′ = X = H), whilst ethanolic sodium hydroxide gave *only* the thiol (V; R = Me, X = H, Y = SH).

Unlike the quinoline derivatives the α-(benziminazolylthio)-propionic and -butyric acid (I; R = Me or Ph, R′ = Me or Et, X = H) did not give anhydro-compounds which could be isolated. With boiling acetic anhydride 3-acetyl-2-thiones (IV; R = Me or Ph, Z = Ac) were obtained, whilst solutions of the acids in cold pyridine and acetic anhydride developed a transitory yellow colour, suggestive of anhydro-compound formation, which was followed by an exothermic reaction, during which 0·5 mol. of carbon dioxide was evolved. A pure product, $C_{30}H_{24}ON_4S_2$, was, however, isolated from only one acid (I; R = Ph, R′ = Et, X = H) and, it is suggested, is the thiol-ester (VI; R = Et) because of its similarity in its chemical properties and ultraviolet absorption to the parent (VI; R = H).

An anhydro-compound was also prepared from (1-methyl-2-glyoxalinylthio)acetic acid. Like the corresponding benziminazole derivatives, this anhydro-compound, although colourless, had an ultraviolet absorption maximum not present in the parent acid. Molecular-weight determinations in water and acetic acid indicate that the anhydro-compound is bimolecular in these solvents.

The differences in chemical reactions of anhydro-(2-benziminazolylthio)acetic acids from those of the analogous quinoline compounds suggest certain differences in the contributions of individual dipolar forms of the two types of anhydro-compounds. Ease of attack by nucleophilic reagents on the compound (III; R = Ph, X = H) at position 2 of the benziminazole and at position 5 of the thiazole ring indicates powerful contributions from the forms (VIII and IX; R = Ph) whilst acid hydrolysis is favoured by a contribution from forms (X) and (XI). It will be noted that the sulphur atom in (IX) bears a negative charge and has a valency shell expanded to ten electrons. The formation of compounds



(VIII) (IX) (X) (XI) (XII)

(VI; R = H or Et) may result from the association of two molecules of the corresponding anhydro-compounds, indicated by molecular-weight determinations.

Like the quinoline analogues,[5] anhydro-(1-phenyl-2-benziminazolylthio)acetic acid in solution shows changes in the position of its longer-wavelength absorption maximum with changes in solvent polarity. It is, however, unlikely that this is due to a powerful contribution from form (XII) as the anhydro-compound shows no maximum indicative of a 2 : 3-dihydrobenziminazole-2-thione, but has the two maxima which are characteristic of the benziminazole ring.

[5] Knott, *J.*, 1955, 940.

Experimental

Absorption maxima were determined in ethanol.

Benziminazolo(2′ : 1′-2 : 3)thiazolid-4-one (II).—(2-Benziminazolylthio)acetic acid [1] (10 g.), pyridine (15 c.c.), and acetic anhydride (10 c.c.) were heated for 10 min. on a steam-bath. On cooling, a solid separated which, on recrystallisation from ethanol, gave the thiazolidone as pale yellow needles, m. p. 181° (5·8 g., 64%) (Found: N, 14·8; S, 16·7. Calc. for $C_9H_6ON_2S$: N, 14·7; S, 16·8%), $\lambda_{max.}$ 2380 (ε 18,900), 2820 (ε 10,300) and 2910 Å (ε 8900).

5-Ethoxymethylenebenziminazolo(2′ : 1′-2 : 3)thiazolid-4-one.—Benziminazolo(2′ : 1′-2 : 3)thiazolid-4-one (9·5 g.), ethyl orthoformate (12 c.c.), and acetic anhydride (15 c.c.) were boiled under reflux for 20 min. and evaporated *in vacuo* to leave a solid. Recrystallisation from ethanol gave the *ethoxymethylene compound* as yellow plates, m. p. 167—169° (5·6 g., 46%) (Found: C, 58·3; H, 3·8. $C_{12}H_{10}O_2N_2S$ requires C, 58·5; H, 4·05%).

5-(2 : 3-Dihydro-3-methyl-2-benzothiazolylidenebenziminazolo(2′ : 1′-2 : 3)thiazolid-4-one.—Benziminazolo(2′ : 1′-2 : 3)thiazolid-4-one (0·475 g.), 2-methylthiobenzothiazole methiodide (0·81 g.), ethanol (25 c.c.), and triethylamine (0·5 c.c.) were boiled for 10 min. Pale yellow crystals separated. Recrystallisation from dioxan gave the *compound* as pale yellow needles, m. p. 330° (0·68 g., 80%) (Found: N, 12·2; S, 19·0. $C_{17}H_{11}ON_3S_2$ requires N, 12·4; S, 19·0%).

The following were obtained similarly: *5-[2-(3-Ethyl-2 : 3-dihydro-2-benzothiazolylidene)-ethylidene]benziminazolo(2′ : 1′-2 : 3)thiazolid-4-one* [from (II) and 2-2′-acetanilidovinylbenzothiazole ethiodide] from dioxan as red needles, m. p. 290° (64%) (Found: N, 10·9; S, 17·1. $C_{20}H_{15}ON_3S_2$ requires N, 11·1; S, 17·0%). The same compound was obtained (56%) from 5-ethoxymethylenebenziminazolo(2′ : 1′-2 : 3)thiazolid-4-one and 2-methylbenzthiazole ethiodide. The *5-[2-(2 : 3-dihydro-3-methyl-2-benzoxazolylidene)ethylidene] analogue* [from (II) and 2-2′-ethylthiovinylbenzoxazole metho-*p*-toluenesulphonate] from dioxan as orange needles, m. p. 318° (60%) (Found: N, 12·0; S, 8·9. $C_{25}H_{19}O_5N_3S$ requires N, 12·15; S, 9·2%). The *5-[2-(1 : 3 : 3-trimethyl-2-indolinylidene)ethylidene] analogue* [from (II) and 2-2′-acetanilidovinyl-3 : 3-dimethylindolenine methiodide] as orange needles (from methanol), m. p. 252° (42%) (Found: N, 11·4; S, 8·6. $C_{23}H_{19}ON_3S$ requires N, 11·3; S, 8·6%). The *5-[2-(1 : 4-dihydro-1-methyl-4-quinolinylidene)ethylidene] analogue* [from (II) and 4-2′-ethylvinylquinoline methiodide] as dark blue plates (from methanol), m. p. 295° (57%) (Found: N, 11·7; S, 9·1. $C_{21}H_{15}ON_3S$ requires N, 11·8; S, 8·95%). The *5-[2-(1 : 2-dihydro-1-methyl-2-quinolinylidene)ethylidene] analogue* [from (II) and 2-2′-ethylthiovinylquinoline methiodide] as dark red microscopic needles (from ethanol), m. p. 339° (67%) (Found: N, 11·95; S, 8·75. $C_{21}H_{15}ON_3S$ requires N, 11·8; S, 8·95%). The *5-benzylidene*, pale yellow plates (from benzene), m. p. 219° (25%) (Found: N, 10·2. $C_{16}H_{10}ON_2S$ requires N, 10·1%), and the *5-p-dimethylaminobenzylidene analogue*, orange needles (from ethanol), m. p. 269° (45%) (Found: N, 13·1. $C_{18}H_{15}ON_3S$ requires N, 13·1%).

2-Hydroxy-1-phenylbenziminazole.—2-Aminodiphenylamine (9·2 g.) and sodium cyanate (3·25 g.) in boiling ethanol (50 c.c.) and 10N-hydrochloric acid (5 c.c.) was boiled for 2 hr., water (200 c.c.) was added, and the precipitated solid was recrystallised from aqueous ethanol, to give *2-ureidodiphenylamine* as colourless plates, m. p. 157° (6·1 g., 53%) (Found: C, 68·5; H, 5·5. $C_{13}H_{13}ON_3$ requires C, 68·7; H, 5·7%). The urea (5 g.) was heated for 1 hr. at 160°, ammonia being evolved. The solid which was obtained recrystallised from ethanol to give *2-hydroxy-1-phenylbenziminazole* as colourless plates, m. p. 204° (2·8 g., 50%) (Found: C, 74·15; H, 4·45; N, 13·1. $C_{13}H_{10}ON_2$ requires C, 74·25; H, 4·7; N, 13·3%).

2-Hydroxy-1-methylbenziminazole.—By a similar process *N-methyl-o-ureidoaniline* (?) was prepared from *N*-methyl-*o*-phenylenediamine and was obtained from aqueous ethanol as plates, m. p. 180° (52%) (Found: C, 58·3; H, 6·7. $C_8H_{11}ON_3$ requires C, 58·2; H, 6·65%). Heating converted it into 2-hydroxy-1-methylbenziminazole, plates (from water), m. p. 188° (70%) (Found: C, 65·0; H, 5·3. Calc. for $C_8H_8ON_2$: C, 64·9; H, 5·4%), identical with the compound prepared from *N*-methyl-*o*-phenylenediamine and carbonyl chloride.[6]

1-Methylbenziminazole-2-thiol.—*N*-Methyl-*o*-nitroaniline (56·8 g.) was dissolved in ethanol (150 c.c.) and 20% aqueous sodium hydroxide (31·5 c.c.), and zinc dust (100 g.) added in portions during 20 min. The mixture was boiled until it became colourless, then filtered hot, and the solid washed with ethanol. Carbon disulphide (48 c.c.) was added to the filtrate and the solution boiled for 4 hr. The solid which separated on cooling recrystallised from ethanol, to give *1-methylbenziminazole-2-thiol* as colourless needles, m. p. 195° (50 g., 83%) (Found: C, 58·4; H,

[6] Pinnow and Sämann, *Ber.*, 1899, **32**, 2190.

4·9; N, 17·2. $C_9H_8N_2S$ requires C, 58·55; H, 4·9; N, 17·5%). Benziminazole-2-thiol (87%) and 1-*phenylbenziminazole-2-thiol*, colourless needles, m. p. 194° (70%), from ethanol (Found: C, 68·65; H, 4·40; N, 12·4. $C_{13}H_{10}N_2S$ requires C, 69·0; H, 4·45; N, 12·4%), were obtained similarly from carbon disulphide with *o*-phenylenediamine and 2-aminodiphenylamine respectively.

1-*Methyl-2-methylthiobenziminazole*.—1-Methylbenziminazole-2-thiol (8·2 g.) in N-sodium hydroxide (50 c.c.) was shaken with methyl iodide (3·2 c.c.) for 1 hr., then extracted with chloroform (3 × 50 c.c.). The chloroform was removed and the residue was distilled, to give 1-*methyl-2-methylthiobenziminazole* as colourless plates, m. p. 56°, b. p. 112—115°/0·8 mm. (6·5 g., 73%) (Found: N, 15·7; S, 18·0. $C_9H_{10}N_2S$ requires N, 15·7; S, 18·0%), $\lambda_{max.}$ 2530 (ε 6500), 2850 (ε 13,600), and 2920 Å (ε 14,200).

1 : 3-*Dimethyl-2-methylthiobenziminazolium iodide* was obtained as colourless needles (from ethanol), m. p. 152° (Found: I, 39·7. $C_{10}H_{13}N_2SI$ requires I, 39·7%), from the above compound by 2 hours' heating with methyl iodide.

2 : 3-*Dihydro*-1 : 3-*dimethyl*-2-*thiobenziminazole*.—The above methiodide (1·5 g.) and pyridine (5 c.c.) were boiled under reflux for 2 hr. The solution was poured into water, and the precipitated solid was recrystallised from ethanol, to give the *thione* as colourless needles, m. p. 153—154° (0·5 g., 63%) (Found: N, 15·55; S, 18·0. $C_9H_{10}N_2S$ requires N, 15·7; S, 18·0%), $\lambda_{max.}$ 2540 (ε 18,100) and 3090 Å (ε 29,500).

1-*Methyl-5-nitrobenziminazole-2-thiol*.—2-Methylamino-5-nitroaniline (28 g.), potassium hydroxide (9·8 g.), 80% ethanol (600 c.c.), and carbon disulphide (28 c.c.) were boiled under reflux for 20 hr. After dilution with water (1 l.), the ethanol was removed by distillation and the hot residue added to N-hydrochloric acid (280 c.c.). This precipitated a solid which was recrystallized from acetic acid to give 1-*methyl-5-nitrobenziminazole-2-thiol* as yellow needles, m. p. 304—305° (decomp.) (30·2 g., 93%) (Found: C, 45·6; H, 3·4. $C_9H_7O_2N_3S$ requires C, 45·8; H, 3·35%).

5-*Nitro*-1-*phenylbenziminazole-2-thiol* was obtained by a similar process from ethanol as yellow needles, m. p. 282° (69%) (Found: C, 57·4; H, 3·3. $C_{13}H_9O_2N_3S$ requires C, 57·5; H, 3·3%).

(1-*Methyl-2-glyoxalinylthio*)*acetic Acid*.—1-Methylglyoxaline-2-thiol (5·7 g.), chloroacetic acid (4·8 g.), and water (20 ml.) were boiled under reflux for 1 hr. N-Sodium hydroxide (50 ml.) was added, the solution evaporated to dryness, and the residue extracted with chloroform (4 × 25 ml.). The chloroform was removed to give an oily *acid* which rapidly solidified and recrystallised from benzene–chloroform as colourless needles, m. p. 85° (7·1 g., 89%) (Found: S, 18·7. $C_8H_8O_2N_2S$ requires S, 18·6%), $\lambda_{max.}$ 2550 Å (20,600).

(2-*Benziminazolylthio*)*acetic Acids* (I).—The following exemplifies the procedure: 1-Methylbenziminazole-2-thiol (16·4 g.) in 10% aqueous sodium hydroxide (40 c.c.), and chloroacetic acid (9·5 g.) in 10% aqueous sodium hydroxide (40 c.c.), were heated together for 2 hr. on the steam-bath. The hot solution was filtered and acidified with concentrated hydrochloric acid (10 c.c.), and the precipitated (1-*methyl*-2-*benziminazolylthio*)*acetic acid* recrystallised from aqueous ethanol as colourless needles, m. p. 190° (16·5 g., 75%) (Found: C, 53·95; H, 4·2. $C_{10}H_{10}O_2N_2S$ requires C, 54·05; H, 4·5%), $\lambda_{max.}$ 2830 (ε 13,400) and 2910 Å (ε 13,900).

Analogous *products* are tabulated.

(2-*Benziminazolylthio*)*acetic acids* (I).

				Yield	Found (%)			Required (%)	
R	R′	X	M. p.	(%)	C	H	Formula	C	H
H [a]	H	H	211° [a]	67	52·0	3·8		Everett [b]	
Ph	H	H	176 [a]	60	62·9	4·45 [c]	$C_{15}H_{12}O_2N_2S$	63·4	4·25
Ph [f]	Me	H	97 [a]	39	61·45	5·0	$C_{16}H_{14}O_2N_2S$	61·50	4·8
Ph	Et	H	87 [a]	32		[d]	$C_{17}H_{16}O_2N_2S$	—	—
Ph	H	NO_2	234—235 [b]	67	54·6	3·6	$C_{15}H_{11}O_4N_3S$	54·7	3·65
Me	H	NO_2	235 [b]	30	44·85	3·1	$C_{10}H_9O_4N_3S$	45·0	3·35

[a] Colourless needles from ethanol. [b] Yellow needles from acetic acid. [c] Found: N, 9·85; S, 11·05. Required: N, 9·85; S, 11·25%. [d] Found: S, 9·65. Required: S, 9·55%. [e] $\lambda_{max.}$ 2480 (ε 6200), 2830 (ε 13,000) and 2910 Å (ε 12,900). [f] $\lambda_{max.}$ 2850 (ε 12,200) and 2930 Å (ε 12,500).

α-(1-*Methyl*-2-*benziminazolylthio*)*butyric Acid*.—α-Bromobutyric acid (9·3 g.) and 1-methylbenziminazole-2-thiol (9·2 g.) were boiled in water (50 c.c.) for 6 hr. After cooling, 40% aqueous

sodium hydroxide (5·5 c.c.) was added to precipitate crystals, which, recrystallised from aqueous ethanol, gave the *acid* as colourless needles, m. p. 132° (7·9 g., 48%) (Found: S, 12·6. $C_{13}H_{12}O_3N_2S$ requires S, 12·7%).

α-(1-*Methyl-2-benziminazolylthio*)*propionic acid* was obtained by a similar process as colourless needles (from water), m. p. 131° (61%) (Found: S, 13·5. $C_{11}H_{10}O_2N_2S$ requires S, 13·6%).

Anhydro-compound from (1-*Methyl-2-glyoxalinylthio*)*acetic Acid.*—The acid (6·0 g.), pyridine (18·0 ml.), and acetic anhydride (6·0 ml.) were warmed on a steam-bath for 5 min. Solid rapidly separated and, after cooling, was filtered off, washed with ether, and recrystallised from water, to give the pure *anhydro-compound* as colourless needles, m. p. 201° (4·25 g., 80%) [Found: C, 46·8; H, 3·8; S, 20·4; *M* (ebullioscopic in H_2O), 249, (in AcOH), 294. $C_6H_6ON_2S$ requires C, 46·7; H, 3·9; S, 20·7%; *M*, 154], $\lambda_{max.}$ in EtOH 2380 (ε 3400) and 3340 (ε 9900), in C_6H_6 3350 (ε 10,900) and in aqueous pyridine (1 : 1) 3370 Å (ε 36,700).

Anhydro-compound from (1-*Methyl-2-benziminazolylthio*)*acetic Acid.*—The acid (5 g.) was dissolved in warm pyridine (15 c.c.), and acetic anhydride (15 c.c.) was added, crystals being precipitated. After 15 min., the *anhydro-compound* was filtered off, washed with acetone, and dried, to give pale yellow needles, m. p. 255° (3·6 g., 78%), insoluble in all the usual solvents (Found: C, 59·05; H, 4·15; N, 13·85; S, 15·15. $C_{10}H_8ON_2S$ requires C, 58·8; H, 3·95; N, 13·7; S, 15·7%).

Anhydro-compound from (1-*Phenyl-2-benziminazolylthio*)*acetic Acid.*—The *anhydro-compound* was obtained (*a*) by a similar process to that above, as pale yellow needles (from a large volume of xylene), m. p. 222° (44%), or (*b*) (64%) by boiling the acid with twice its weight of acetic anhydride [Found: C, 67·6; H, 3·9; N, 10·0; S, 11·7; *M* (Rast), 269, (ebullioscopic in AcOH), 1200 ± 100. $C_{15}H_{10}ON_2S$ requires C, 67·65; H, 3·8; N, 10·5; S, 12·0%; *M*, 266], $\lambda_{max.}$ in EtOH 2550 (ε 12,000), 2860 (ε 7900), 2930 (ε 7800), and 3500 (ε 9700), in dioxan 2700 (ε 11,500), 2870 (ε 7500), 2940 (ε 7500), and 3600 (ε 7500), in C_6H_6 2880 (ε 8100), 2950 (ε 8200), and 3655 (ε 6950), and in aqueous pyridine (1 : 1) 2920 (ε 6850) and 3520 Å (ε 10,500). By similar reactions *anhydro-*(1-*methyl-5-nitro-2-benziminazolylthio*)*acetic acid* as orange needles, m. p. 238° (decomp.) (81%) (Found: C, 48·1; H, 2·9. $C_{10}H_7O_3N_3S$ requires C, 48·3; H, 2·8%), and *anhydro-*(5-*nitro-*1-*phenyl-2-benziminazolylthio*)*acetic acid* as yellow needles, m. p. 221° (62%) (Found: C, 57·75; H, 2·8. $C_{15}H_9O_3N_3S$ requires C, 57·8; H, 2·9%), were also prepared.

Action of Aqueous Sulphuric Acid on Anhydro-compound from (1-*Phenyl-2-benziminazolylthio*)*acetic Acid.*—The anhydro-compound (5·0 g.) was heated at 100° with 50% aqueous sulphuric acid (20 c.c.), the solid dissolving with evolution of carbon dioxide. Water (100 c.c.) was added, the mixture extracted with benzene (2 × 100 c.c.), and the benzene solution extracted successively with (*a*) 2N-sodium carbonate which gave, on acidification, (1-phenyl-2-benziminazolylthio)acetic acid (0·87 g., 18%), and (*b*) N-sodium hydroxide, from which 1-phenylbenziminazole-2-thiol (0·03 g.) was obtained. Removal of benzene gave a sticky solid which crystallised (2·6 g., 56%) on addition of ethanol. Recrystallisation from benzene–ethanol gave 1-*phenyl-2-benziminazolyl* α-(1-*phenyl-2-benziminazolylthio*)*thiolacetate* (VI; R = H) as colourless plates which became pink in air, m. p. 176° (2·1 g.) (Found: C, 68·7; H, 4·15; N, 10·8; S, 12·8. $C_{28}H_{20}ON_4S_2$ requires C, 68·4; H, 4·05; N, 11·4; S, 12·95%), $\lambda_{max.}$ 2500 (ε 24,800), 2850 (ε 21,800), and 2920 Å (ε 21,500). The compound (2·0 g.), when boiled for 1 hr. with 10% ethanolic sodium hydroxide, gave 1-phenylbenziminazole-2-thiol (0·7 g., 76%) and (1-phenyl-2-benziminazolylthio)acetic acid (1·0 g., 86%).

Under similar conditions, the anhydro-compounds from (1-methyl- and 5-nitro-1-phenyl-2-benziminazolylthio)acetic acid gave the parent acids only, in yields of 87% and 92% respectively.

Action of Nitric Acid on Anhydro-compound from (1-*Phenyl-2-benziminazolylthio*)*acetic Acid.*—The anhydro-compound (2·5 g.), water (80 c.c.), and nitric acid (*d* 1·41; 10 c.c.) were boiled under reflux for 1 hr. Nitrous fumes were evolved, and the resulting solution was cooled to give a crystalline precipitate which was filtered off. Recrystallisation from aqueous ethanol gave 2-*hydroxy-5-nitro-*1-*phenylbenziminazole* as pale yellow plates, m. p. 239—240° (1·2 g., 47%) (Found: C, 60·95; H, 3·6. $C_{13}H_9O_3N_3$ requires C, 61·2; H, 3·55%), identical with the compound obtained (45%) similarly from anhydro-(5-nitro-1-phenyl-2-benziminazolylthio)-acetic acid. The original acid filtrate was basified, to give an oil which gave 1-*phenylbenziminazole picrate* as yellow plates (from ethanol), m. p. 182° (1·6 g., 41%) (Found: N, 16·4. $C_{13}H_{10}N_2.C_6H_3O_7N_3$ requires N, 16·55%), identical with the picrate obtained from 1-phenylbenziminazole.[7]

By a similar process the anhydro-compound from (1-methyl-2-benziminazolylthio)acetic acid

[7] Phillips, *J.*, 1929, 2823.

gave 1-methylbenziminazole picrate, m. p. and mixed m. p. 244° (28%), and 2-hydroxy-1-methyl-5-nitrobenziminazole as yellow needles (from acetic acid), m. p. 302° (31%) (Found: C, 49·6; H, 3·7. Calc. for $C_8H_7O_3N_3$: C, 49·7; H, 3·65%), identical with the compound described by Romburgh and Huyser[8] and that obtained (40%) from anhydro-(1-methyl-5-nitro-2-benziminazolylthio)acetic acid and dilute nitric acid.

By similar reactions with dilute nitric acid, (*a*) 1-phenylbenziminazole-2-thiol gave 1-phenylbenziminazole as picrate (80%), (*b*) 2-hydroxy-1-phenylbenziminazole gave 2-hydroxy-5-nitro-1-phenylbenziminazole (63%), and (*c*) (1-phenyl-2-benziminazolylthio)acetic acid was recovered (83%).

Action of Alkali on the Anhydro-compound from (1-Phenyl-2-benziminazolylthio)acetic Acid.—The anhydro-compound (2·5 g.) was boiled for 1 hr. with 40% aqueous sodium hydroxide (10 c.c.) and ethanol (20 c.c.). Water (200 c.c.) was added, the ethanol removed, and the solution saturated with carbon dioxide to precipitate a solid which recrystallised from aqueous ethanol as colourless needles, m. p. 161° (1·8 g., 88%) [Found: C, 71·85; H, 4·95; N, 13·55; S, 7·4; *M* (Rast), 228. Calc. for $C_{15}H_{10}N_2S + C_{15}H_{10}ON_2$: C, 71·55; H, 4·65; N, 12·85; S, 7·35%; *M* (average of hydroxy- and mercapto-compounds), 218]. This substance was identical with the equimolar eutectic from 2-hydroxy-1-phenylbenziminazole and 1-phenylbenziminazole-2-thiol either by dissolution in alkali and reprecipitation with acid, or by recrystallisation from aqueous ethanol or benzene–light petroleum. The eutectic mixture was also obtained (81%) together with the parent acid (3%) by the prolonged action of boiling 10% aqueous sodium carbonate on the anhydro-compound.

By a similar process, anhydro-(1-methyl-2-benziminazolylthio)acetic acid gave 1-methylbenziminazole-2-thiol only (68%).

Reduction of Anhydro-compound from (1-Phenyl-2-benziminazolylthio)acetic Acid.—Granulated zinc (5·0 g.) was added to the anhydro-compound (5·0 g.), ethanol (50 c.c.), and concentrated hydrochloric acid (20 c.c.). A vigorous reaction took place with evolution of hydrogen sulphide, methanethiol, and carbon dioxide. The solution obtained was diluted with water to give 1-phenylbenziminazole-2-thiol (3·1 g., 75%).

Action of Benzylamine on the Anhydro-compound from (1-Phenyl-2-benziminazolylthio)acetic Acid.—The anhydro-compound (5·5 g.) and benzylamine (10 g.) were boiled under reflux for 1 hr. The solid dissolved, and hydrogen sulphide was evolved. The yellow solution, diluted with water (100 c.c.), gave an oil which was dissolved in ether and extracted with 2% aqueous sodium hydroxide. Acidification of the alkaline extracts gave benziminazole-2-thiol (2·2 g., 47%), whilst evaporation of the ether gave a brown solid (2·5 g., 45%) which, recrystallised from ethanol, gave *2-benzylamino-1-phenylbenziminazole*, colourless needles, m. p. 145° (1·49 g., 25%) (Found: C, 80·35; H, 5·75; N, 13·9. $C_{20}H_{17}N_3$ requires C, 80·3; H, 5·7; N, 14·0%). Benzylamine, with the parent acid under similar conditions, gave 2-benzylamino-1-phenylbenziminazole (77%), but 1-phenylbenziminazole-2-thiol was recovered (88%) after 2 hours' boiling with excess of benzylamine.

Action of Acetic Anhydride on α-(1-Phenyl-2-benziminazolylthio)butyric Acid.—The acid (2·0 g.) and acetic anhydride (10 c.c.) were boiled for 1 hr. under reflux. The anhydride was removed *in vacuo* and the residue was recrystallised from acetone, to give *3-acetyl-2 : 3-dihydro-1-phenyl-2-thiobenziminazole* as colourless needles, m. p. 191° (0·7 g., 41%) (Found: C, 67·15; H, 4·5; S, 11·75; N, 10·1. $C_{16}H_{12}ON_2S$ requires C, 67·2; H, 4·5; S, 11·95; N, 10·4%), $\lambda_{max.}$ 3120 Å (ε 20,800). The same compound was obtained (78% and 50%) from acetic anhydride and 1-phenylbenziminazole-2-thiol or α-(1-phenyl-2-benziminazolylthio)propionic acid respectively. *3-Acetyl-2 : 3-dihydro-1-methyl-2-thiobenziminazole* was obtained (72%, 15%, and 28%) similarly from acetic anhydride and 1-methylbenziminazole-2-thiol, α-(1-methyl-2-benziminazolylthio)propionic acid, or α-(1-methyl-2-benziminazolylthio)butyric acid. It recrystallised from acetone as colourless needles, m. p. 144° (Found: C, 58·0; H, 4·8; S, 15·6. $C_{10}H_{10}ON_2S$ requires C, 58·1; H, 4·85; S, 15·5%), $\lambda_{max.}$ 2410 (ε 17,100) and 3100 Å (ε 21,500).

Action of Acetic Anhydride and Pyridine on α-(1-Phenyl-2-benziminazolylthio)butyric Acid.—The acid (5·0 g.) was dissolved in pyridine (6 c.c.), and acetic anhydride (5 c.c.) added, affording a yellow solution. Carbon dioxide was slowly evolved (170 c.c.) whilst the temperature rose to 41·5° and the colour gradually disappeared. The solution was cooled, to give colourless crystals (3·07 g., m. p. 145°) which gave *1-phenyl-2-benziminazolyl α-(1-phenyl-2-benziminazolylthio)thiolbutyrate* (VI; R = Et) from benzene–light petroleum as colourless plates, m. p. 147° [Found:

[8] Romburgh and Huyser, *Verslag. k. Akad. Wetenschap. Amsterdam, Afd. Natuurh.*, 1926, **35**, 665. *Chem. Abs.*, 1927, **21**, 382.

C, 69·1; H, 4·45; S, 12·45; *M* (ebullioscopic in C_6H_6), 507. $C_{30}H_{24}ON_4S$ requires C, 69·2; H, 4·6; S, 12·3%; *M*, 520], $\lambda_{max.}$ 2420 (ε 22,000), 2850 (ε 19,400), and 2920 Å (ε 18,600). When boiled with 10% alcoholic sodium hydroxide (5 c.c.) it (1 g.) gave α-(1-phenyl-2-benziminazolylthio)butyric acid (0·42 g., 70%), and 1-phenylbenziminazole-2-thiol (0·37 g., 85%); boiling acetic anhydride converted it into 3-acetyl-2:3-dihydro-1-phenyl-2-thiobenziminazole (68%).

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Renwick Laboratory, Ilford Limited, Ilford. [*Received, July 18th*, 1955.]

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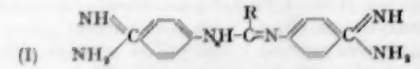
75. *The Search for Chemotherapeutic Amidines. Part XII.** NN′-*Di(amidinophenyl)amidines.*

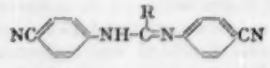
By E. Crundwell.

Some *NN′*-di(amidinophenyl)amidines, and some vinylogues of *NN′*-di(amidinophenyl)formamidine have been prepared and found to have slight trypanocidal activity.

During systematic investigation of the effect on trypanocidal activity of varying the central link between two *p*-amidinophenyl groups the preparation of compounds of type (I) was investigated. Such amidines appear not to have been described though Peyron and Peyron [1] reported a failure to prepare *N*-*p*-amidinophenyl-*N′*-phenylacetamidine from the corresponding nitrile, because of the difficulty of separating the very soluble amidine salt from ammonium chloride.



(I)



(II)

The amidines (I; R = Me, Et, or Ph) were prepared from the nitriles (II) which were obtained from the reaction of *p*-aminobenzonitrile with benzotrichloride (giving II; R = Ph) or with *N*-(*p*-cyanophenylimidoyl chlorides (giving II; R = Me and Et). Attempted condensation of anilides with *p*-aminobenzonitrile, using phosphorus trichloride [2] or phosphoric oxide,[1] gave only unchanged material.

The dinitriles (II) were converted into the diamidines (I) by Pinner's method. It was found that if the imidoate did not separate within 24 hours it was slowly hydrolysed and only *p*-aminobenzamidine was isolated on subsequent treatment with alcoholic ammonia.

NN′-Di-(*p*-cyanophenyl)formamidine was obtained from *p*-aminobenzonitrile and triethyl orthoformate. This nitrile (II; R = H) decomposed on treatment with alcoholic hydrogen chloride. The reaction of *p*-aminobenzamidine hydrochloride with triethyl orthoformate gave a product for which analyses corresponded approximately to those calculated for the desired diamidine (I; R = H); this product was however rapidly hydrolysed in aqueous solution to *p*-formamidobenzamidine hydrochloride. These observations are in agreement with the acid-catalysed hydrolysis [3] of *NN′*-diphenylformamidine:

$$Ph{\cdot}NH{\cdot}CH{:}NPh \longrightarrow Ph{\cdot}NH_2 + Ph{\cdot}NH{\cdot}CHO$$

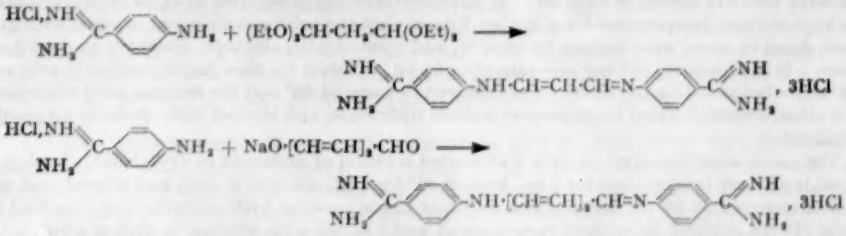
One nuclear-substituted amidine of type (I) was prepared. Bromination of *p*-acetamidobenzonitrile by Bogert and Wise's procedure [4] gave a dibromo-derivative. Bromination of *p*-aminobenzonitrile in chloroform–pyridine gave a monobromo-derivative which on acetylation gave a product corresponding to that described by Bogert and Wise.[4]

* Part XI, *J.*, 1951, 2588.

[1] Peyron and Peyron, *Bull. Soc. chim.* (*France*), 1953, 851.
[2] Sen and Rây, *J.*, 1926, 646.
[3] De Wolfe and Roberts, *J. Amer. Chem. Soc.*, 1953, **75**, 2942.
[4] Bogert and Wise, *ibid.*, 1912, **34**, 693.

Condensation of this 4-amino-3-bromobenzonitrile with *N*-*p*-cyanophenylacetimidoyl chloride gave *N'*-3-bromo-4-cyanophenyl-*N*-*p*-cyanophenylacetamidine, which was converted into the corresponding di(amidinophenyl)amidine by Pinner's method.

Two vinylogues of *NN'*-di-(*p*-amidinophenyl)formamidine were prepared by condensation of *p*-aminobenzamidine hydrochloride with malondialdehyde bisdiethyl acetal or with monosodium glutacondialdehyde in dilute hydrochloric acid :



These two diamidines, and three compounds of type (I) where R = Me, Et, and Ph, were examined for activity against trypanosome infections in mice. The most active compound (I; R = Me) was curative against *T. rhodesiense* [LD_{50}/CD_{50} = 10 (chemotherapeutic ratio = 10)] and *T. congolense* (ratio = 3) infections, but was ineffective in *T. evansi* infections. It was of no prophylactic value in *T. congolense* infections. The remaining compounds were less active or inactive. The compound (I; R = Me) had no antifungal activity *in vitro*.

Experimental

NN'-Di-(p-*cyanophenyl)benzamidine.*—*p*-Aminobenzonitrile (2·4 g., 0·02 mole), benzotrichloride (1·5 ml., 0·01 mole), nitrobenzene (10 ml.), and stannic chloride (0·1 ml.) were heated together at 160—170° for 30 min. A white solid separated; the mixture was cooled and diluted with alcohol (20 ml.), and the solid was collected, washed with alcohol, and ether, and dried at 75° (3·2 g.). It was then dissolved in pyridine (32 ml.); the solution was filtered and the filtrate added to water (32 ml.) with stirring, to give a yellow solid which was collected, washed with water, alcohol, and ether, and dried at 75° to a yellow powder (2·2 g., 69%), m. p. 198—200°. This amidine crystallised from alcohol as yellow prisms, m. p. 201—202° (Found : C, 78·2; H, 4·7; N, 17·0. $C_{21}H_{14}N_4$ requires C, 78·25; H, 4·35; N, 17·4%). Omission of stannic chloride caused the yield to fall to 40%.

NN'-Di-(p-*cyanophenyl)formamidine.*—*p*-Aminobenzonitrile (2·4 g., 0·02 mole) and triethyl orthoformate (1·8 ml., 0·01 mole) were heated on a steam-bath. A clear solution was formed which soon became solid, with the evolution of ethanol. Heating was continued for 30 min., then the crude solid crystallised from alcohol (125 ml.) as white feathery needles (1·7 g., 70%), m. p. 216—217° (Found : C, 73·5; H, 4·3; N, 22·7. $C_{15}H_{10}N_4$ requires C, 73·2; H, 4·1; N, 22·7%). A similar *amidine* was obtained when the reaction was carried out in acetic acid at room temperature.

NN'-Di-(p-*cyanophenyl)acetamidine.*—*p*-Acetamidobenzonitrile (1·6 g., 0·01 mole) was added to a cold solution of phosphorus pentachloride (2·1 g., 0·01 mole) in dry benzene (20 ml.). The mixture was refluxed, forming a clear solution after 5 min. Refluxing was continued for 10 min., then the hot solution was filtered and the solvent removed *in vacuo* at 50°. The residual solid was dissolved in hot dry benzene (20 ml.), and a solution of *p*-aminobenzonitrile (1·2 g., 0·01 mole) in hot dry benzene (10 ml.) was added with stirring. A white solid separated. The mixture was stirred and refluxed for 3 hr.; it was then cooled and the solid was collected, washed with light petroleum, and dried at 75°. The white powder (2·2 g.) was dissolved in pyridine (22 ml.); the solution was filtered and water (44 ml.) added to the filtrate to give a white precipitate which was filtered off, washed well with water, and dried at 75°. The white crystalline *product* (1·7 g., 65%), m. p. 216°, crystallised from benzene (100 ml./g.) or dioxan (5 ml./g.) as needles, m. p. 218° (Found : C, 73·6; H, 4·7. $C_{16}H_{12}N_4$ requires C, 73·9; H, 4·5%).

NN'-Di-(p-*cyanophenyl)propionamidine* was similarly prepared (64%) from *p*-propionamidobenzonitrile and crystallised from alcohol (10 ml./g.) as needles, m. p. 178—179° (Found : C, 74·5; H, 5·35; N, 20·2. $C_{17}H_{14}N_4$ requires C, 74·5; H, 5·1; N, 20·4%).

N′-2-*Bromo*-4-*cyanophenyl*-N-p-*cyanophenylacetamidine*, similarly prepared (50%) from *p*-acetamidobenzonitrile and 4-amino-3-bromobenzonitrile and crystallised from alcohol (20 ml./g.), had m. p. 184° (Found: C, 57·5; H, 3·65; Br, 23·1. $C_{16}H_{11}N_4Br$ requires C, 56·6; H, 3·25; Br, 23·6%).

NN′-*Di*-(p-*amidinophenyl*)*amidines*.—*General procedure*. The appropriate dinitrile was dissolved in dry chlorform (10—20 ml./g.), dry alcohol (2 ml./g.) added, and the solution saturated with dry hydrogen chloride. If an imidoate began to separate after 24 hr. the mixture was kept at room temperature for a further 7 days, then the solid was collected, washed with dry ether, dried *in vacuo* over sodium hydroxide, and treated with alcoholic ammonia as described below. If the imidoate did not separate after 24 hr., to avoid the slow decomposition in solution to *p*-aminobenzamidine the solvent was removed *in vacuo* at 50° and the residual solid triturated with ether, collected, dried *in vacuo* over sodium hydroxide, and treated with alcoholic ammonia as follows.

The crude ester was treated with a saturated solution of ammonia in dry alcohol (4 ml./g.), set aside at room temperature for 1 hr., kept at 55° for 6 hr., allowed to cool, and filtered, and the alcohol removed at 50° *in vacuo*. The resultant crude amidine hydrochloride was dissolved in water (10 ml./g.) and 2N-sodium carbonate (3 mol.) added with stirring to give a white solid which was collected, washed well with water to remove inorganic material and dried *in vacuo*. This solid was suspended in dry alcohol (10 ml./g.), and a saturated solution of dry hydrogen chloride in dry alcohol (1 ml./g.) added to give a yellow solution to which dry ether was added, precipitating a cream-coloured solid. This procedure was the only one by which the crude amidine could be freed from ammonium chloride. Yields were 30—70%. Like many of the diamidine salts described in the previous papers of this series, these amidine salts were strongly hygroscopic when thoroughly dried. To obtain a stable hydrate they were kept overnight in a closed vessel over water before analysis.

In this way were prepared:

NN′-*Di*-(p-*amidinophenyl*)*acetamidine trihydrochloride*, amorphous, decomp. above 300° [Found: C, 46·9; H, 5·35; N, 20·35; Cl, 26·9; loss at 100°/20 mm., 1·35; H_2O (Karl Fischer), about 1·0. $C_{16}H_{18}N_6.3HCl,\frac{1}{2}H_2O$ requires C, 47·0; H, 5·3; N, 20·6; Cl, 26·1; H_2O, 1·1%].

NN′-*Di*-(p-*amidinophenyl*)*propionamidine trihydrochloride*, amorphous, decomp. about 265° (Found: C, 48·7; H, 5·5; N, 19·6. $C_{17}H_{20}N_6.3HCl,\frac{1}{2}H_2O$ requires C, 48·4; H, 5·6; N, 19·9%).

NN′-*Di*-(p-*amidinophenyl*)*benzamidine trihydrochloride*, amorphous, m. p. above 300° (Found: C, 53·1; H, 5·5; N, 17·3; Cl, 22·7. $C_{21}H_{20}N_6.3HCl,\frac{1}{2}H_2O$ requires C, 53·1; H, 5·05; N, 17·65; Cl, 22·5%).

N′-4-*Amidino*-2-*bromophenyl*-N-p-*amidinophenylacetamidine dihydrochloride* was prepared similarly but crystallised from the alcoholic ammonia. It was therefore not purified *via* the base but by crystallisation from water (10 ml./g.) as needles, decomp. 295—296° (Found: C, 41·3; H, 4·6; N, 18·1; Br, 17·1; Cl^-, 15·8. $C_{16}H_{17}N_6Br,2HCl,H_2O$ requires C, 41·35; H, 4·5; N, 18·1; Br, 17·2; Cl, 15·4%).

p-Aminobenzamidine hydrochloride was prepared similarly, but the crude amidine was purified by crystallisation from 17% aqueous sodium chloride and then alcohol, to give flakes, m. p. 221—222°. (Easson and Pyman[3] give m. p. 225—226° for a product prepared by reduction of *p*-nitrobenzamidine.)

Reaction between p-*Aminobenzamidine Hydrochloride and Triethyl Orthoformate*.—*p*-Aminobenzamidine hydrochloride (20 g.) was boiled with butanol (750 ml.); the hot solution was filtered and triethyl orthoformate (9 ml.) was added. The solution was refluxed for 90 min., a yellow solid separating. The hot mixture was filtered and the solid NN′-*di*-p-*amidinophenylformamidine dihydrochloride* washed with butanol and ether and dried *in vacuo*. The yellow powder, m. p. 265° (Found: C, 50·5; H, 5·35; N, 24·2. $C_{15}H_{16}N_6,2HCl$ requires C, 51·0; H, 5·1; N, 23·8%), crystallised from water as needles, m. p. 292°, probably p-*formamidobenzamidine hydrochloride* (Found: C, 48·0; H, 5·3; N, 20·9. $C_8H_9ON_3,HCl$ requires C, 48·1; H, 5·0; N, 21·1%).

1-p-*Amidinoanilino*-3-p-*amidinophenyliminoprop*-1-*ene Trihydrochloride*.—*p*-Aminobenzamidine dihydrochloride (41·6 g., 0·2 mole) was dissolved in 0·5N-hydrochloric acid (400 ml.). The solution was heated on a steam-bath and stirred while malondialdehyde bisdiethyl acetal (40 ml., 0·1 mole) was added; a yellow solid started to separate. Stirring and heating were continued for 3 hr. After cooling, the solid was filtered off, washed with dilute hydrochloric

[3] Easson and Pyman, *J.*, 1931, 2994.

acid, alcohol, and ether, and dried *in vacuo*. The *salt* (25·7 g., 62%) crystallised from dilute hydrochloric acid as yellow needles, m. p. about 265° (decomp.) [Found: C, 44·15; H, 5·95; N, 17·9; Cl, 22·6; loss at 100°/20 mm., 11·4; H_2O (Karl Fischer), about 11·8. $C_{17}H_{18}N_6$, 3HCl,3H_2O requires C, 44·2; H, 5·8; N, 17·9; Cl, 22·6; H_2O, 11·5%].

1-p-*Amidinoanilino*-5-p-*amidinophenyliminopenta*-1 : 3-*diene Trihydrochloride*.—*p*-Aminobenzamidine dihydrochloride (21 g., 0·1 mole) was dissolved in water, and a solution of the monosodium derivative of glutacondialdehyde dihydrate (7·8 g., 0·05 mole) in water (150 ml.) was added to give a deep red solution which was kept for 15 min. 2N-Hydrochloric acid (25 ml.) was then added to give a red solid which was filtered off, triturated with alcohol, washed with ether, and dried *in vacuo*, giving a red amorphous *product*, decomp. about 240° (15·6 g., 56%) (Found: C, 41·75; H, 6·35; N, 15·4. $C_{19}H_{20}N_6$,3HCl,6H_2O requires C, 41·5; H, 6·4; N, 15·3%).

4-*Amino*-3-*bromobenzonitrile*.—*p*-Aminobenzonitrile (5·9 g., 0·05 mole) was dissolved in chloroform (50 ml.), and pyridine (4 ml.) added. The solution was stirred vigorously and bromine (2·5 ml., 0·05 mole) in chloroform (50 ml.) was added during 1 hr. The solution was then washed with water (2 × 250 ml.), and the chloroform removed to give a brown solid (8·8 g.). This *nitrile* crystallised from water as needles (5·35 g., 54%), m. p. 109—111° (Found: N, 14·3; Br, 40·9. $C_7H_5N_2Br$ requires N, 14·2; Br, 40·65%).

I thank Mrs. R. Stone, B.Sc., and Mr. S. Squires for the biological results, Mr. S. Bance, B.Sc., A.R.I.C., for the semimicroanalyses, Mr. N. Jones for technical assistance, and the Directors of May and Baker Ltd. for permission to publish these results.

Research Laboratories, May and Baker Ltd.,
Dagenham, Essex. [*Received, July 22nd*, 1955.]

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76. *Peptides. Part V.* Condensation of the γ-Carboxyl Group of α-Glutamyl Peptides with the Peptide Chain.*

By D. W. Clayton, G. W. Kenner, and R. C. Sheppard.

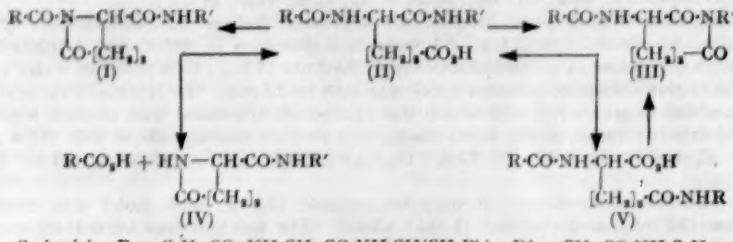
Condensation of α-glutamyl peptide derivatives (II) through the action of thionyl chloride and a tertiary amine may lead to either an oxopyrrolidine (I) or a dioxopiperidine (III), depending on the structure of the peptide. In the two cases studied, namely, (I*c*) and (VI), alkaline hydrolysis of the oxopyrrolidine largely regenerated the α-glutamyl compound. Alkaline hydrolysis of the dioxopiperidines, (III*a*) and (III*b*), regenerated a little of the starting material (II) but the main product was the γ-glutamyl isomer (V).

Methods for selective degradation of polypeptides into two or more smaller peptides would be valuable.[1,2] The aim of the present work was to cleave the acyl–glutamyl link in α-glutamyl peptides (II) by formation of a 1-acyl-2-oxopyrrolidine (I), followed by alkaline hydrolysis. It was expected that the hydrolysis would give the oxopyrrolidine (IV), since mixed anhydrides of α-acylamino-acids and simple carboxylic acids are attacked by amines at the more cationoid carbonyl group derived from the acylamino-acid.[3] Our results show, however, that the six-membered ring imide (III) may be produced in preference to the five-membered ring imide (I),[4] and that, even when the latter is produced, its hydrolysis may give predominantly the original peptide (II); therefore the method is unlikely to be useful. On the other hand the hydrolysis of the six-membered ring imides (III) follows the expected course and gives mainly the γ-glutamyl isomer (V) of the original α-glutamyl peptide (II) (cf. discussion by Battersby and Robinson [3]).

* Part IV, *J.*, 1953, 673.

[1] Elliott, *Biochem. J.*, 1952, **50**, 542; Sanger, *Adv. Protein Chem.*, 1952, **7**, 11.
[2] Battersby and Robinson, *J.*, 1955, 259.
[3] Wieland, Kern, and Sehring, *Annalen*, 1950, **569**, 117; Vaughan and Osato, *J. Amer. Chem. Soc.*, 1951, **73**, 5553; Wieland and Stimming, *Annalen*, 1953, **579**, 97.
[4] Clayton and Kenner, *Chem. and Ind.*, 1953, 1205.

As a substance of type (II) toluene-*p*-sulphonylglycyl-L-phenylalanyl-α-L-glutamylglycine *cyclo*hexylamide (II*a*) was selected; the preparation of this and other starting materials is discussed below. Treating the acid (II*a*) in dimethylformamide with 1 mol.



Series (*a*) : R = $C_7H_7·SO_2·NH·CH_2·CO·NH·CH(CH_2Ph)$; R′ = $CH_2·CO·NH·C_6H_{11}$.
Series (*b*) : R = Ph, R′ = $CH_2·CO·NH·C_6H_{11}$.
Series (*c*) : R = $C_7H_7·SO_2·NH·CH_2·CO·NH·CH_2$; R′ = $CH(CH_2Ph)·CO·NH·C_6H_{11}$.

each of pyridine and thionyl chloride (to give the acid chloride [5]) and then with a second portion of pyridine gave a crystalline condensation product in 74% yield, and 22% of (II*a*) was recovered. Hydrolysis of the neutral substance with dilute alkali furnished 9% of the original acid and 90% of the isomeric γ-glutamyl derivative (V*a*), identical with a sample produced by unambiguous synthesis. The structural relation of the two acids was confirmed by electrometric titration; compounds of type (V) are considerably stronger acids than those of type (II) owing to the proximity of the carboxyl and an amide group.[6]

The conversion of the α- (II*a*) into the γ-glutamyl derivative (V*a*) requires the dioxopiperidine structure (III*a*) for the neutral intermediate, so preparation of such imides was investigated by using the more accessible benzoyl-α-DL-glutamylglycine *cyclo*hexylamide (II*b*). The crystalline dioxopiperidine (III*b*) was obtained in good yield in the manner already described or by substituting ethyl chloroformate [7] for thionyl chloride. Simple dissolution of the acid (II*b*) in excess of acetic anhydride yielded 76% (after these experiments had been completed the preparation of dioxopiperidines by means of hot acetic anhydride was reported [8]). In contrast with these successful preparations through mixed anhydrides with carboxylic acids, reaction between triethylamine and the mixed anhydride with lithium hydrogen sulphate [9] furnished only traces of the dioxopiperidine, and these may have arisen through disproportionation of the mixed into the symmetrical anhydride.

Alkaline hydrolysis of the dioxopiperidine (III*b*) gave a mixture of the α-glutamyl compound (II*b*) (13%) and the γ-isomer (V*b*) (85%), which was easily resolved by countercurrent distribution; the latter acid, being the stronger, was preferentially retained by a phosphate buffer. Battersby and Robinson [3] found that the action of alkali on the ethyl ester of an acid differing from (II*b*) merely in the substitution of an *n*-hexyl for the *cyclo*hexyl residue gave a 4 : 5 mixture of the acids corresponding to (II*b*) and (V*b*). It now appears likely that the route of this hydrolysis was only partly through the dioxopiperidine, as was envisaged by Battersby and Robinson as one possible explanation of their results.

Direct α ⟶ γ-isomerisation of (II*b*) into (V*b*) by a combined process of cyclisation and ring-opening was also attempted : tetraethyl pyrophosphate, a water-soluble anhydride which was moderately efficient in anhydrous dioxan, was used in aqueous alkaline solution, but at best only 32% of the γ-acid was obtained. One cause of the low yield was doubtless the reversibility of the process, for the dioxopiperidine (III*b*) was formed in good yield from (V*b*) by the thionyl chloride method.

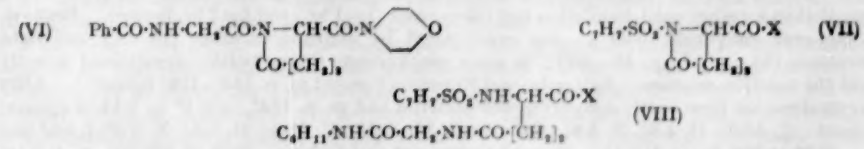
A third series of experiments was undertaken to test the possibility that the benzyl group of the phenylalanyl residue in (II*a*) had sterically hindered the formation of the

[5] Human and Mills, *Nature*, 1948, **158**, 877.
[6] Cohn and Edsall, "Proteins, Amino Acids and Peptides," Reinhold, New York, 1943, p. 134.
[7] Boissonas, *Helv. Chim. Acta*, 1951, **34**, 874; Vaughan, *J. Amer. Chem. Soc.*, 1951, **73**, 3547.
[8] Kovács, Medzihradszky, and Bruckner, *Naturwiss.*, 1954, **41**, 450.
[9] Kenner and Stedman, *J.*, 1952, 2069.

oxopyrrolidine (I*a*) [in (II*b*) the benzamido-group was not a suitable model for the peptide chain]. Cyclisation of toluene-*p*-sulphonylglycylglycyl-α-L-glutamyl-L-phenylalanine *cyclo*hexylamide (II*c*) by the thionyl chloride process gave an excellent yield of a non-crystalline neutral material, but alkaline hydrolysis of this regenerated the α-compound (II*c*) in 90% yield with no trace of the expected γ-isomer (V*c*). It was difficult to account for this result by invoking selective steric hindrance by the benzyl group of the hydrolysis of the dioxopiperidine (III*c*). It seemed more likely that the neutral intermediate was the oxopyrrolidine (I*c*) and that our initial assumption about the behaviour of such imides was incorrect. Indeed the potential lability of the oxopyrrolidine ring had been demonstrated in the ammonolysis of 1-acetyl-2-oxopyrrolidine-5-carboxylic acid to acetylglutamine.[10] A closer analogy which also supported our view was provided by the behaviour of a non-crystalline imide prepared from benzoylglycyl-α-L-glutamylmorpholine, which must have been 1-benzoylglycyl-5-morpholinocarbonyl-2-oxo-L-pyrrolidine (VI) in absence of the hydrogen necessary for dioxopiperidine formation. Alkaline hydrolysis of this oxopyrrolidine gave mainly the acid from which it had been prepared, together with some benzoylglycine. It would have been interesting to examine the cyclisation, which would not be sterically hindered in either direction, of toluene-*p*-sulphonyglycylglycyl-α-L-glutamylglycine *cyclo*hexylamide but work with this series of compounds was abandoned because of their excessive water-solubility, a property which they share with the morpholides mentioned above. However, we believe that our results establish the general courses, which will be controlled by structural influences in any instance, of the condensation and subsequent hydrolysis of α-glutamyl peptide derivatives.

Preparation of compounds of series (*b*) started from benzoyl-DL-glutamic anhydride, which was obtained from benzoyl-L-glutamic acid and acetic anhydride. Racemisation occurs likewise during anhydride formation from *p*-nitrobenzoyl- and phenylacetyl-L-glutamic acid,[11] but is absent in the dehydration of benzyloxycarbonyl- and phthaloyl-L-glutamic acid.[12] The racemic anhydrides must have been produced from the isomeric oxazolones, but, as has been shown in the other two cases,[13] the oxazolone structure cannot be assigned to the material obtained from benzoyl-L-glutamic acid. It shows negligible ultraviolet absorption at 250 mμ, and has an infrared doublet at 1770, 1818 cm.$^{-1}$ while lacking a band in the carbonyl region (1700—1750 cm.$^{-1}$). Moreover reaction between the anhydride and glycine *cyclo*hexylamide in chloroform solution gave a **6 : 7** mixture of benzoyl-α-DL-glutamylglycine *cyclo*hexylamide and the γ-isomer.

The other starting materials with the α-glutamyl structure were prepared from γ-benzyl hydrogen L-glutamate, preferably by acylating a suspension of the ester in aqueous dimethylformamide with the mixed sulphuric anhydride [9] of the appropriate acylamino-acid; despite the sparing solubility of γ-benzyl hydrogen L-glutamate the yields were about 50%. The resultant carboxylic acids were condensed with an amine by the sulphuric anhydride method, and finally the benzyl protecting group was removed by hydrogenolysis. The γ-glutamyl derivative (V*a*) was prepared by sulphuric anhydride acylation of γ-L-glutamylglycine *cyclo*hexylamide, which was obtained from 1-toluene-*p*-sulphonyl-2-oxo-



L-pyrrolidine-5-carboxylic acid (VII; X = OH) by interaction with glycine *cyclo*hexylamide followed by sodium–liquid ammonia treatment of the resultant amide (VIII; X = OH). We are greatly indebted to Dr. J. M. Swan, who informed us of this general

[10] J. A. King and McMillan, *J. Amer. Chem. Soc.*, 1952, **74**, 2859.
[11] F. E. King and Spensley, *J.*, 1950, 3159; Baker and Jones, *J.*, 1951, 1143.
[12] Bergmann and Zervas, *Ber.*, 1932, **65**, 1192; F. E. King and Kidd, *J.*, 1949, 3315.
[13] Swan, *Australian. J. Sci. Res.*, 1952, **5**, *A*, 721; J. A. King, McMillan, and Genzer, *J. Amer. Chem. Soc.*, 1952, **74**, 5202.

method before its publication.[14, 15] Application of the method to the synthesis of α-L-glutamylglycine *cyclo*hexylamide was less successful. Reaction between a chloroform solution of 1-toluene-*p*-sulphonyl-2-oxo-L-pyrrolidine-5-carbonyl chloride (VII; X = Cl) and a solution of glycine *cyclo*hexylamide in aqueous sodium hydrogen carbonate furnished a neutral oil in good yield, but alkaline hydrolysis of this gave, in addition to the expected toluene-*p*-sulphonyl-α-L-glutamylglycine *cyclo*hexylamide, small amounts of the γ-isomer (VIII; X = OH) and of toluene-*p*-sulphonyl-αγ-L-glutamyldi(glycine *cyclo*hexylamide) (VIII; X = $NH{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}C_6H_{11}$). Formation of the last product signifies attack by the amine at the oxopyrrolidinecarbonyl group. If some of this attack occurred *before* the attack at the carbonyl of the acid chloride group, the resultant acid chloride (VIII; X = Cl) would cyclise easily to a dioxopiperidine, which would contaminate the desired product (VII; X = $NH{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}C_6H_{11}$) in the neutral fraction and give rise to some (VIII; X = OH) on hydrolysis. Alternative explanations based on the assumption of side-reactions during the alkaline hydrolysis of (VII; X = $NH{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}C_6H_{11}$) can be produced. Rudinger [15] likewise obtained a mixture from the reaction of the acid chloride (VII; X = Cl) with glycine in sodium hydrogen carbonate solution, but Swan and du Vigneaud [14] were able to couple the acid chloride satisfactorily with asparagine in presence of an aqueous suspension of magnesium oxide.

Experimental

M. p.s are corrected. pK_{MCS} is defined on p. 380.

Analytical samples were dried for 6 hr. at 80°/1 mm. over phosphoric oxide, unless otherwise stated. Evaporations were carried out under reduced pressure. Solutions in dimethylformamide of the lithium, potassium, and trimethylphenylammonium salts of acyl sulphates were prepared according to the general procedure of Kenner and Stedman.[9] When these solutions were used to acylate an amino-compound in aqueous solution, they were dropped slowly in an atmosphere of dry nitrogen into the aqueous solution of the amino-compound, which also contained an indicator; during this process N-sodium hydroxide was added simultaneously so as to maintain the colour of the indicator at that corresponding to the specified pH. *m*-Cresol-purple, thymol-blue, and phenolphthalein were used as indicators of pH 8·0, 8·7, and 9·0 respectively.

γ-Benzyl Hydrogen L-*Glutamate* (cf. ref. 16).—A solution of L-glutamic acid (44·2 g.) and toluene-*p*-sulphonic acid (54·7 g.) in benzyl alcohol (217 c.c.) was distilled at 120° (bath-temp.)/2 mm. during 1½ hr. The concentrated residue crystallised when triturated with ether in a mortar. The solid was dried, and dissolved in benzyl alcohol (217 c.c.) together with toluene-*p*-sulphonic acid (2 g.). The processes of distillation and crystallisation were then repeated. Addition of diethylamine (34 c.c.) to a solution of the resultant salt in ethanol (600 c.c.) precipitated γ-benzyl hydrogen L-glutamate, which recrystallised from water (1 l.) in plates (30·7 g., 43%), m. p. 176—176·5°, $[\alpha]_D^{18}$ +19·3° (*c*, 1·14 in acetic acid), pK_1 2·7, pK_2 9·1 (in water) (Found: C, 61·0; H, 6·6; N, 6·3. Calc. for $C_{12}H_{15}O_4N$: C, 60·8; H, 6·4; N, 5·9%).

*Benzoyl-*DL-*glutamic Anhydride.*—Benzoyl-L-glutamic acid (1 g.) and acetic anhydride (8 c.c.) were shaken together until dissolution had taken place (½—1 hr.) and for 2 hr. further. Benzoyl-DL-glutamic anhydride (0·65 g.) was precipitated by addition of ether (15 c.c.) and light petroleum (25 c.c.; b. p. 40—60°); in some preparations the anhydride crystallised directly from the reaction mixture. Battersby and Robinson [2] record m. p. 154—155° (uncorr.). After recrystallisation from acetic anhydride, our material had m. p. 153°, $[\alpha]_D^{16}$ 0° (*c*, 2·14 in dioxan) (Found: C, 62·0; H, 4·8; N, 5·8. Calc. for $C_{12}H_{11}O_4N$: C, 61·8; H, 4·8; N, 6·0%), and had $\varepsilon_{max.}$ 9470 at 226 mμ in dioxan. Benzoyl-L-glutamic acid had $\varepsilon_{max.}$ 9680 at 225 mμ in dioxan.

Benzyloxycarbonylglycine cyclo*Hexylamide.*—*cyclo*Hexylamine (45 c.c.) was added to a solution of trimethylphenylammonium benzyloxycarbonylglycyl sulphate (30 mmoles) in dimethylformamide (75 c.c.) and the mixture was kept for 1 hr. at 20°. The ethyl acetate solution, obtained by evaporation of the solvent and partition of the residue between ethyl acetate and 3N-hydrochloric acid, was washed with water and saturated sodium hydrogen

[14] Swan and du Vigneaud, *ibid.*, 1954, **76**, 3110.
[15] Rudinger, *Coll. Czech. Chem. Comm.*, 1954, **19**, 375.
[16] Miller and Waelsch, *J. Amer. Chem. Soc.*, 1952, **74**, 1092.

carbonate solution before being dried and evaporated. The cyclo*hexylamide* (7·8 g., 90%) crystallised from ethyl acetate–light petroleum (b. p. 40—60°) in needles, m. p. 110° (Found: C, 66·1; H, 7·9; N, 9·8. $C_{18}H_{22}O_3N_2$ requires C, 66·2; H, 7·6; N, 9·7%).

Glycine cyclo*Hexylamide Hydrobromide.*—A solution of benzyloxycarbonylglycine *cyclo*hexylamide (2·22 g.) in N-hydrogen bromide in acetic acid (23·1 c.c.) was heated on a steam-bath until evolution of carbon dioxide ceased (10 min.). Addition of ether (200 c.c.) to the cold solution caused crystallisation of the *hydrobromide* (1·76 g., 96%), m. p. 186·5° unaltered by recrystallisation from ethanol–ether (Found: C, 40·8; H, 7·5; N, 11·5. $C_8H_{17}ON_2Br$ requires C, 40·5; H, 7·2; N, 11·8%).

*Benzoyl-*DL-(α *and* γ)-*glutamylglycine* cyclo*Hexylamides* (II*b*) *and* (V*b*).—Benzoyl-DL-glutamic anhydride (3·49 g., 15 mmoles) was added in several portions during 30 min. to a swirled and cooled solution of glycine *cyclo*hexylamide hydrobromide (3·55 g., 15 mmoles) and triethylamine (2·1 c.c., 15 mmoles) in chloroform (40 c.c.). Next day 3N-hydrochloric acid (20 c.c.) and more chloroform (40 c.c.) were added. The layers were separated and the aqueous layer was re-extracted with chloroform (20 c.c.). The material in the chloroform extracts was distributed (counter-current) between ethyl acetate and a phosphate buffer (0·8M-KH_2PO_4; 0·2M-K_2HPO_4) (10 transfers; 100 c.c. phases). Tubes 3—8 contained *benzoyl-*DL-α-*glutamylglycine* cyclo*hexylamide* (*K* 1·5; 2·60 g., 45%), which was recrystallised from aqueous ethanol and had m. p. 193°, pK_{MCS} 6·1 (Found: C, 61·8; H, 6·7; N, 10·9. $C_{20}H_{27}O_5N_3$ requires C, 61·7; H, 7·0; N, 10·8%). Tubes 0—3 contained *benzoyl-*DL-γ-*glutamylglycine* cyclo*hexylamide* (*K* 0·12; 3·06 g., 53%), which was recrystallised several times from aqueous ethanol and had m. p. 175·5°, pK_{MCS} 5·4 (Found: C, 61·9; H, 6·6; N, 11·1%).

*Benzoyl-*DL-*glutamoylglycine* cyclo*Hexylamide* (III*b*).—A solution of benzoyl-DL-α-glutamylglycine *cyclo*hexylamide (0·389 g., 1 mmole) in dioxan (100 c.c.) was concentrated to 40 c.c., a 20 cm. Fenske fractionating column being used. Thionyl chloride (0·08 c.c., 1 mmole), pyridine (0·09 c.c., 1 mmole), and after 40 min. further pyridine (0·09 c.c., 1 mmole), were added to the cooled solution. At the second stage pyridine hydrochloride was precipitated. The mixture was kept for 1 hr. before addition of water (2 c.c.) and evaporation of the solvents. The residue was dissolved in a mixture of butan-1-ol (50 c.c.) and ethyl acetate (50 c.c.), which was extracted with saturated sodium hydrogen carbonate solution (2 × 25 c.c.) and water (25 c.c.). Evaporation of the dried (Na_2SO_4) extract gave the crystalline *dioxopiperidine* (0·369 g., 99%), which, recrystallised from aqueous ethanol, had m. p. 261·5—262·5° (decomp.) (Found: C, 64·9; H, 6·9; N, 11·1. $C_{20}H_{25}O_4N_3$ requires C, 64·7; H, 6·8; N, 11·3%).

The dioxopiperidine was also obtained when the thionyl chloride was replaced by ethyl chloroformate (95% yield) or by tetraethyl pyrophosphate (1 equiv. giving 67%, 2 equivs. giving 89%). In the last case recovery was complicated by the presence of excess of neutral pyrophosphate. Solution of the α-glutamyl peptide in excess of cold acetic anhydride also yielded the dioxopiperidine (76%). Treatment of the lithium salt of the α-glutamyl peptide with 1 equiv. of the sulphur trioxide–dimethylformamide complex followed by triethylamine (1 equiv.) gave only 6% of the dioxopiperidine, 83% of the starting material being recovered.

Treatment of benzoyl-DL-γ-glutamylglycine *cyclo*hexylamide with thionyl chloride and pyridine also gave the dioxopiperidine (93%).

*Hydrolysis of Benzoyl-*DL-*glutamoylglycine* cyclo*Hexylamide* (III*b*).—A solution of the dioxopiperidine (0·346 g.) in dioxan (25 c.c.) and 4N-sodium hydroxide (5 c.c.) was kept for 15 min. at 20° and then acidified and evaporated. The residue was distributed between ethyl acetate (25 c.c.) and 3N-hydrochloric acid (25 c.c.), which was then extracted with ethyl acetate (6 × 50 c.c.). The mixture of the benzoyl-DL-(α and γ)-glutamylglycine *cyclo*hexylamides obtained by evaporating the dried ethyl acetate extracts was distributed (counter-current) in the same way as during their preparation. This gave the α-isomer (0·048 g., 13%) and the γ-isomer (0·308 g., 85%) with the correct m. p.s. Their identity was also established by chromatography in ethyl acetate on paper which had been sprayed with phosphate buffer (0·4M-KH_2PO_4; 0·6M-K_2HPO_4) [ascending R_F 0·50 (α), 0·08 (γ)].

*Isomerisation of Benzoyl-*DL-α-*glutamylglycine* cyclo*Hexylamide in Aqueous Solution by Means of Tetraethyl Pyrophosphate.*—The α-glutamyl peptide (0·389 g., 1 mmole) was dissolved in dimethylformamide (2·5 c.c.) and tetraethyl pyrophosphate (2·5 c.c., 10 mmoles). To this was added a solution of potassium hydrogen carbonate (1·17 g., 11 mmoles) in water (5 c.c.), and the mixture was left for 14 days with intermittent shaking. It was then made alkaline (phenolphthalein) with sodium hydroxide solution and, after 1 hr. further, worked up as in the foregoing experiment. The counter-current distribution separated the recovered starting material (0·235 g., 63%) from its γ-isomer (0·094 g., 25%).

When more pyrophosphate (50 mmoles) was used, only 36% of the starting material was recovered together with 32% of the γ-isomer. Substitution of zinc oxide (0·36 g., 11 mmoles) for the potassium hydrogen carbonate afforded 0·078 g. (20%) of the γ-peptide. When excess of pyridine was used instead, no isomerisation was detected.

Benzyloxycarbonyl-α-L-glutamylglycine cyclo*Hexylamide γ-Benzyl Ester.*—Ethyl chloroformate (0·68 c.c., 7·15 mmoles) was added to a solution of γ-benzyl hydrogen benzyloxycarbonyl-L-glutamate [17] (2·65 g., 7·15 mmoles) and triethylamine (0·99 c.c., 7·15 mmoles) in dioxan (15 c.c.), which was kept at 10°. A precipitate of triethylamine hydrochloride appeared immediately. After 10 min. a mixture of glycine *cyclo*hexylamide hydrobromide (1·7 g., 7·15 mmoles), triethylamine (7·15 mmoles), and dioxan (15 c.c.) was added. Next day the solvents were evaporated and the residue was treated with ethyl acetate (40 c.c.) and 3N-hydrochloric acid (10 c.c.). The majority of the product crystallised and was collected after having been washed in suspension with hydrochloric acid, water, and sodium hydrogen carbonate solution. The remainder was recovered from the ethyl acetate. The *dipeptide derivative* (3·2 g., 88%) was recrystallised from ethanol and had m. p. 173·5—174·5°, $[\alpha]_D^{15.5}$ +2·5° (*c*, 1·7 in dimethylformamide) (Found : C, 65·8; H, 6·5; N, 8·4. $C_{20}H_{25}O_6N_3$ requires C, 66·0; H, 6·9; N, 8·3%).

α-L-Glutamylglycine cyclo*Hexylamide.*—Hydrogen was bubbled for 4 hr. through a stirred suspension of palladium black in dioxan (15 c.c.) and 95% ethanol (20 c.c.) containing the foregoing dipeptide derivative (3·38 g., 6 mmoles). The catalyst was removed and washed with warm water. Evaporation of the filtrate and washings followed by addition of ethanol furnished *α-L-glutamylglycine* cyclo*hexylamide* (1·3 g., 62%), m. p. 158° (decomp.), $[\alpha]_D^{16.5}$ +50·4° (*c*, 1·15 in N-HCl) (Found : C, 54·7; H, 8·1; N, 14·5. $C_{13}H_{23}O_4N_3$ requires C, 54·7; H, 8·1; N, 14·7%).

*Toluene-*p*-sulphonylglycyl-L-phenylalanyl-α-L-glutamylglycine* cyclo*Hexylamide* (II*a*).—α-L-glutamylglycine *cyclo*hexylamide (5 mmoles) was acylated at pH 8·7 by potassium toluene-*p*-sulphonylglycyl-L-phenylalanyl sulphate (5 mmoles), prepared from toluene-*p*-sulphonylglycyl-L-phenylalanine [18] (m. p. 160·5°). The reaction mixture was brought to pH 6 and evaporated at 50°/2 mm. Almost all the product crystallised directly when ethyl acetate (40 c.c.) and 3N-hydrochloric acid (5 c.c.) were added to the residue, and the remainder was recovered by ethyl acetate extraction (4 × 60 c.c.) of the aqueous layer, evaporation of the combined ethyl acetate solutions, and trituration with light petroleum. The *tetrapeptide derivative* (2·26 g., 71%), recrystallised from ethanol, had m. p. 219·5—220·5° (decomp.), $[\alpha]_D^{16}$ −9·1° (*c*, 1·25 in EtOH), pK_{MCS} 6·2 (Found : C, 57·6; H, 6·1; N, 10·8. $C_{31}H_{41}O_9N_5S$ requires C, 57·8; H, 6·4; N, 10·9%). Repetition of the acylation process with the aqueous liquor of the above extraction and a fresh portion (1·5 mmoles) of the sulphate anhydride afforded a further 0·36 g. (11%) of the tetrapeptide derivative.

*Toluene-*p*-sulphonylglycyl-L-phenylalanyl-L-glutamoylglycine* cyclo*Hexylamide* (III*a*).—A solution of toluene-*p*-sulphonylglycyl-L-phenylalanyl-α-L-glutamylglycine *cyclo*hexylamide (II*a*) (0·322 g., 0·5 mmole) in dimethylformamide (40 c.c.) was concentrated to 7 c.c., a 20 cm. Fenske fractionating column at 50°/14 mm. being used. Pyridine (0·05 c.c., 0·62 mmole), thionyl chloride (0·044 c.c., 0·62 mmole), and, 1 hr. later, more pyridine (0·05 c.c.) were added to the solution, which was kept at 20° for 2 hr. in all before the addition of water (2 c.c.). Next day the solution was evaporated and the residue was distributed between saturated sodium hydrogen carbonate solution and ethyl acetate, which was extracted with a second portion of hydrogen carbonate solution. The *dioxopiperidine* (0·231 g., 74%) was obtained by evaporation of the ethyl acetate and was recrystallised from ethanol, m. p. 214·5° (Found : C, 59·75; H, 6·55; N, 11·1. $C_{31}H_{39}O_7N_5S$ requires C, 59·5; H, 6·3; N, 11·2%). Some starting material (0·072 g., 22%) was recovered by acidification of the sodium hydrogen carbonate solutions.

Treatment of the potassium salt of the amide (II*a*) with 1 equiv. of the sulphur trioxide–dimethylformamide complex followed by 1 equiv. of triethylamine afforded only 10% of neutral material, m. p. 170—178°, which was shown by recrystallisation to be impure (III*a*); 82% of the original acid was recovered.

A solution of (II*a*) (0·286 g.) in thionyl chloride (0·5 c.c.) was kept at 19° for 5 min. before evaporation at 50°. Benzene was thrice distilled from the yellow residue, which was resolved into an acidic fraction (0·160 g.) and a neutral fraction (0·120 g.). Recrystallisation of the latter from ethanol gave a 30% yield of the product (III*a*).

*Toluene-*p*-sulphonylglycyl-L-phenylalanyl-γ-L-glutamylglycine* cyclo*Hexylamide* (V*a*) *from*

[17] Hanby, Waley, and Watson, *J.*, 1950, 3245.
[18] Clayton, Kenner, *et al.*, unpublished work.

(III*a*).—A solution of the dioxopiperidine (III*a*) (0·022 g.) in 0·5N-sodium hydroxide (1 c.c.) was kept for 10 min. at 18° and then acidified. The crystalline precipitate was taken up in ethyl acetate, which was washed with water before extraction with sodium hydrogen carbonate solution. The alkaline solution was acidified and extracted with ethyl acetate, which was evaporated to a crystalline residue of the *γ-glutamyl derivative* (0·020 g., 90%), m. p. 173° after recrystallisation from ethyl acetate (Found: C, 57·9; H, 6·4; N, 10·9. $C_{31}H_{41}O_8N_5S$ requires C, 57·8; H, 6·4; N, 10·9%). In an experiment on a larger scale, 9% of the isomeric α-glutamyl derivative separated when ethanol was used for the initial crystallisation. Ascending paper chromatography in butan-1-ol saturated with 2N-ammonia separated the dioxopiperidine (III*a*) (R_F 0·80), the γ-glutamyl derivative (V*a*) (R_F 0·53), and the α-isomer (II*a*) (R_F 0·61).

*Toluene-*p*-sulphonyl-γ-*L*-glutamylglycine* cyclo*Hexylamide* (VIII; X = OH).—A solution of 1-toluene-*p*-sulphonyl-2-oxo-L-pyrrolidine-5-carboxylic acid (VII; X = OH) [19] (2·80 g., 10 mmoles), glycine *cyclo*hexylamide hydrobromide (2·50 g., 10·5 mmoles), and triethylamine (3·08 c.c., 22 mmoles) in acetonitrile (20 c.c.) was boiled under reflux for 3·5 hr. and then evaporated. The residue was dissolved in N-sodium hydroxide (40 c.c.), which was washed with ethyl acetate (2 × 50 c.c.). Acidification of the ice-cold aqueous layer yielded the crystalline *dipeptide derivative* (3·53 g., 81%), m. p. 199—200° after recrystallisation from aqueous ethanol, $[\alpha]_D^{20}$ −5·8° (*c*, 2 in 0·1N-NaOH), pK_{MCS} 5·2 (Found: C, 54·4; H, 6·6; N, 9·8. $C_{20}H_{29}O_6N_3S$ requires C, 54·7; H, 6·6; N, 9·6%).

γ-L-Glutamylglycine cyclo*Hexylamide*.—Sodium was added to a solution of the foregoing toluene-*p*-sulphonyl derivative (VIII; X = OH) (2·95 g.) in liquid ammonia (300 c.c.) until the blue colour persisted for 10 min. Dowex-50 ion-exchange resin (18 g.) in the ammonium salt form was added and the mixture was left in an open flask. Next day the last traces of ammonia were removed by vacuum-evaporation and water (25 c.c.) was added to the residue. The resin was removed by filtration and washed with water (35 c.c.). The combined aqueous solutions were clarified by filtration through Hyflo Supercel, were brought to pH 6 by addition of a few drops of acetic acid and were diluted with ethanol (200 c.c.). The small quantity of inorganic material, which separated when the solution was kept overnight at 0°, was removed and the product (1·98 g.), m. p. 171—176° with preliminary softening, was precipitated by addition of ether (1 l.). It could neither be crystallised nor obtained analytically pure, although it gave a single spot of R_F 0·32, detected by ninhydrin, on paper chromatography in butan-1-ol saturated with 3N-ammonia.

*Toluene-*p*-sulphonylglycyl-L-phenylalanyl-γ-L-glutamylglycine* cyclo*Hexylamide* (V*a*).—Lithium toluene-*p*-sulphonylglycyl-L-phenylalanyl sulphate (1 mmole) was brought into reaction with γ-L-glutamylglycine *cyclo*hexylamide (1 mmole) at pH 8. The resulting solution was brought to pH 6 by addition of 3N-hydrochloric acid and evaporated. The solution of the residue in 3N-hydrochloric acid (10 c.c.) was extracted with ethyl acetate (6 × 50 c.c.), which was dried and evaporated. Crystallisation of the glassy residue from ethyl acetate furnished the tetrapeptide derivative (0·430 g., 67%), m. p. 169—170°, pK_{MCS} 5·5 (Found: N, 10·6. Calc. for $C_{31}H_{41}O_8N_5S$: N, 10·9%). This material was indistinguishable by infrared spectrography or paper chromatography from that prepared by hydrolysis of the dioxopiperidine (III*a*) (see above).

Benzyloxycarbonyl-L-phenylalanine cyclo*Hexylamide*.—This *compound* was prepared in 65% yield in a manner similar to that previously described for the glycine analogue. It had m. p. 165°, $[\alpha]_D^{20}$ −1·2° (*c*, 1·6 in dimethylformamide) (Found: C, 72·3; H, 7·5; N, 7·6. $C_{23}H_{28}O_3N_2$ requires C, 72·6; H, 7·4; N, 7·4%).

L-*Phenylalanine* cyclo*Hexylamide*.—A solution of the foregoing benzyloxycarbonyl derivative (4·9 g., 13 mmoles) in acetic acid (32 c.c.) containing hydrogen bromide (40 mmoles) was heated on a steam-bath until the evolution of carbon dioxide ceased (15 min.) and was then evaporated. The acidic solution of the residue in water (150 c.c.) was washed with ethyl acetate (2 × 50 c.c.) and then brought to pH 9 by addition of dilute aqueous sodium hydroxide. The precipitated cyclo*hexylamide* was extracted into ethyl acetate (3 × 100 c.c.) and then crystallised in needles (2·5 g., 82%), m. p. 101—102°, $[\alpha]_D^{23}$ +19·7° (*c*, 3·4 in EtOH) (Found, in material dried at 50°: C, 73·2; H, 9·0; N, 11·6. $C_{15}H_{22}ON_2$ requires C, 73·1; H, 9·0; N, 11·4%).

*γ-Benzyl Toluene-*p*-sulphonylglycylglycyl-L-glutamate*.—A suspension of γ-benzyl hydrogen L-glutamate (2 mmoles) in 50% aqueous dimethylformamide was acylated at pH 8·5 by lithium toluene-*p*-sulphonylglycylglycyl sulphate (2 mmoles). The resultant clear solution was kept for 30 min. before acidification (pH 6) and evaporation. The product was separated from the

[19] Rudinger, *Coll. Czech. Chem. Comm.*, 1954, **19**, 369.

residue by dissolution in 3N-hydrochloric acid and extraction with ethyl acetate (3 × 25 c.c.). Counter-current distribution (20 transfers; 20 c.c. phases) between ethyl acetate and a phosphate buffer (0·8M-KH_2PO_4; 0·2M-K_2HPO_4) afforded the *γ-benzyl ester* (0·512 g., 52%), K 1·8 (tubes 8—18), which crystallised from ethyl acetate–light petroleum (b. p. 40—60°) in platelets, m. p. 101—103°, pK_{MCS} 5·4, $[\alpha]_D^{22}$ +9·4° (*c*, 3·7 in EtOH) (Found: C, 54·4; H, 5·1; N, 8·4. $C_{32}H_{37}O_8N_3S$ requires C, 54·6; H, 5·4; N, 8·3%). Toluene-*p*-sulphonylglycylglycine (0·172 g., 32%), m. p. 175°, K 0·065, was recovered from tubes 0—3.

Toluene-p-*sulphonylglycylglycyl*-α-L-*glutamyl*-L-*phenylalanine* cyclo*Hexylamide* γ-*Benzyl Ester*.—A solution of L-phenylalanine *cyclo*hexylamide (0·246 g., 1 mmole) and triethylamine (0·14 c.c., 1 mmole) in dimethylformamide (5 c.c.) was added to a dimethylformamide solution (10 c.c.) of lithium toluene-*p*-sulphonylglycylglycyl-α-L-glutamyl sulphate γ-benzyl ester (1 mmole). Next day the solution was evaporated and the residue was distributed between ethyl acetate (200 c.c.) and N-hydrochloric acid (20 c.c.). Evaporation of the ethyl acetate, after it had been washed with more N-hydrochloric acid, saturated sodium hydrogen carbonate solution, and water, yielded the *γ-benzyl ester* (0·599 g., 82%), m. p. 195—200° (Found: C, 62·0; H, 6·3; N, 9·8. $C_{38}H_{47}O_8N_5S$ requires C, 62·2; H, 6·4; N, 9·5%).

Toluene-p-*sulphonylglycylglycyl*-α-L-*glutamyl*-L-*phenylalanine* cyclo*Hexylamide* (II*c*).—The foregoing γ-benzyl ester (1·5 g.) was hydrogenated at atmospheric pressure and 20° with palladium black catalyst in dimethylformamide (50 c.c.) and water (5 c.c.). The calculated quantity of hydrogen was absorbed in 2·5 hr. The catalyst was removed and the solvent evaporated. The residue was taken up in saturated sodium hydrogen carbonate solution (75 c.c.), which was washed with ethyl acetate (50 c.c.). The *carboxylic acid* (1·15 g., 82%) was precipitated by acidification of the carbonate solution and, after recrystallisation from aqueous ethanol, had m. p. 188·5—190°, pK_{MCS} 6·1, $[\alpha]_D^{21}$ −22·0° (*c*, 3 in dimethylformamide) (Found: C, 57·5; H, 6·1; N, 11·1. $C_{31}H_{41}O_8N_5S$ requires C, 57·8; H, 6·4; N, 10·9%).

Dehydration of the cyclo*Hexylamide* (II*c*) *and its Regeneration from the Condensation Product*.—A solution of the tetrapeptide derivative (II*c*) (0·645 g., 1 mmole) in dioxan (300 c.c.) was concentrated under reduced pressure to about 200 c.c. and then cooled to 10°. When triethylamine (0·17 c.c., 1·2 mmoles) and thionyl chloride (0·087 c.c., 1·2 mmoles) were added, a precipitate of triethylamine hydrochloride appeared. After 20 min. a second similar portion of triethylamine was added and, 1 hr. later, water (2 c.c.) also. The solution was evaporated and the residue distributed between butan-1-ol (100 c.c.), ethyl acetate (100 c.c.), and water (25 c.c.). The organic layer was washed with sodium hydrogen carbonate solution (2 × 50 c.c.) and water (2 × 50 c.c.) before being evaporated. The resulting neutral material (0·626 g., 100%), m. p. 177—179° (decomp.), was an amorphous powder; its infrared spectrum is recorded below.

This neutral material (0·308 g., 0·5 mmole) was dissolved in dimethylformamide (10 c.c.) and water (5 c.c.), and treated with N-sodium hydroxide (0·6 c.c.). After 1 hr. the solution was acidified (pH 6) and evaporated. The residue crystallised easily when ethyl acetate (40 c.c.) and M-potassium phosphate buffer (40 c.c.) were added. The mixed solvents were acidified with phosphoric acid (3 c.c.) and removed, leaving the product (II*c*) (0·245 g.), m. p. 184°, and more (0·038 g., 90% in all) was recovered from the ethyl acetate. The substance was identified by m. p. (raised to 187—189° by recrystallisation from aqueous ethanol), mixed m. p., and paper chromatography in butan-1-ol saturated with 3N-ammonia (R_F 0·78), which failed to disclose the presence of any other acidic substance even in the crystallisation liquors.

γ-Benzyl Hydrogen Toluene-p-*sulphonylglycyl*-L-*phenylalanyl*-L-*glutamate*.—A solution of γ-benzyl hydrogen L-glutamate (2·4 mmoles) in formamide (14 c.c.) and water (10 c.c.) was acylated at pH 9 by potassium toluene-*p*-sulphonylglycyl-L-phenylalanyl sulphate (2 mmoles). The resulting solution was neutralised with dilute sulphuric acid and evaporated. The product was extracted with ethyl acetate (6 × 50 c.c.) from 3N-hydrochloric acid (30 c.c.). Evaporation yielded a formamide-containing syrup, which crystallised on addition of water. The *tripeptide ester* (0·54 g., 45%) was recrystallised from ethyl acetate–light petroleum (b. p. 40—60°) and had m. p. 146—147°, pK_{MCS} 5·5, $[\alpha]_D^{15}$ −20·9° (*c*, 2 in EtOH) (Found: C, 60·7; H, 5·7; N, 7·2. $C_{30}H_{33}O_8N_3S$ requires C, 60·5; H, 5·6; N, 7·1%).

γ-Benzyl Hydrogen Benzoylglycyl-L-*glutamate*.—A suspension of γ-benzyl hydrogen L-glutamate (22 mmoles) in 50% aqueous dimethylformamide was acylated with lithium benzoylglycyl sulphate (20 mmoles) at pH 9. The resulting clear solution was kept for 30 min. before being acidified (pH 6) with dilute sulphuric acid and evaporated. The residue was distributed between ethyl acetate (100 c.c.) and 3N-sulphuric acid (50 c.c.) which was further extracted with ethyl acetate (50 c.c.). The material in the ethyl acetate layers was distributed (14 transfers; 100 c.c. phases) between ethyl acetate and phosphate buffer (0·8M-KH_2PO_4; 0·2M-K_2HPO_4).

γ-Benzyl hydrogen benzoylglycyl-L-glutamate (5·21 g., 65%), m. p. 136—137·5° after recrystallisation from ethyl acetate, pK_{MCS} 5·3, $[\alpha]_D^{21}$ −6·85° (*c*, 1·6 in dimethylformamide) (Found: C, 63·6; H, 5·8; N, 7·35. $C_{21}H_{22}O_6N_2$ requires C, 63·3; H, 5·6; N, 7·0%), was recovered from tubes 4—12 (*K* 1·50). Tubes 0—3 contained benzoylglycine (0·94 g., 25%).

Benzoylglycyl-α-L-glutamylmorpholine.—Morpholine (5 c.c.) was added to a solution of lithium benzoylglycyl-α-L-glutamyl sulphate γ-benzyl ester (8 mmoles) in dimethylformamide (75 c.c.), which was then kept for 1 hr. at 20° before being evaporated. The residue was distributed between N-sulphuric acid (50 c.c.) and ethyl acetate (200 c.c.), which was washed successively with N-sulphuric acid (50 c.c.), water (50 c.c.), sodium hydrogen carbonate solution (3 × 50 c.c.), and water (50 c.c.). Evaporation of the dried (Na_2SO_4) ethyl acetate solution furnished a syrupy benzyl ester (2·53 g., 68%), which was shaken in 95% ethanol (200 c.c.) with palladium black catalyst and hydrogen until uptake of the latter reached that theoretically required (7 hr.). The material obtained by filtration and evaporation was distributed between ethyl acetate (75 c.c.) and N-sodium carbonate which was then acidified and repeatedly extracted with ethyl acetate (500 c.c. in all). The *morpholide* (1·345 g., 67%) crystallised slowly when very dilute hydrochloric acid was added to the residue from evaporation of the ethyl acetate. It was recrystallised from water and had m. p. 117—118°, pK_{MCS} 6·1 (Found: C, 57·6; H, 6·4; N, 10·9. $C_{18}H_{23}O_6N_3$ requires C, 57·3; H, 6·1; N, 11·1%).

Formation and Hydrolysis of 1-Benzoylglycyl-5-morpholinocarbonyl-2-oxo-L-pyrrolidine (VI).—Triethylamine (0·21 c.c., 1·5 mmoles) and thionyl chloride (0·11 c.c., 1·5 mmoles) were added to a solution of benzoylglycyl-α-L-glutamylmorpholine (0·511 g., 1·35 mmoles) in dioxan (50 c.c.), which had been dried by concentration from 120 c.c. A second equal portion of triethylamine was added after 30 min. and this was followed after 1·5 hr. by water (2 c.c.). The solvents were evaporated and the residue was dissolved in butan-1-ol, which was then washed with dilute hydrochloric acid and aqueous sodium hydrogen carbonate; the aqueous washings were back-extracted with butanol. Evaporation of the combined butanol extracts left the neutral fraction as a pale yellow glass (0·379 g., 78%), which was hydrolysed by N-sodium hydroxide (1·6 c.c.) and water (10 c.c.). After 1 hr. the solution was acidified and evaporated to dryness. Paper chromatography of the residue in butanol saturated with 3N-ammonia showed that the predominating product was the original benzoylglycyl-α-L-glutamylmorpholine (R_F 0·26); a smaller quantity of benzoylglycine (R_F 0·33) was also detected.

Toluene-p-sulphonyl-α-L-glutamylglycine cyclo*Hexylamide and Toluene-p-sulphonyl-αγ-L-glutamyldi(glycine* cyclo*Hexylamide).*—Glycine *cyclo*hexylamide hydrobromide (3·076 g., 13 mmoles), sodium hydrogen carbonate (2·18 g., 26 mmoles), and water (25 c.c.) were added successively to a solution of 1-toluene-*p*-sulphonyl-2-oxo-L-pyrrolidine-5-carbonyl chloride [14] (3·70 g., 12·2 mmoles) in chloroform (50 c.c.) at 0°. The flask was shaken vigorously until the evolution of carbon dioxide had ceased (5 min.) and was then left for 30 min. further at 0°. The chloroform layer was then washed with sodium hydrogen carbonate solution (2 × 25 c.c.) and N-hydrochloric acid (2 × 25 c.c.) before being evaporated. N-Sodium hydroxide (10 c.c.) was added to the cold (0°) solution of the resulting neutral oil (4·04 g., 80%) in dimethylformamide (40 c.c.), which was kept for 30 min. before being acidified (pH 6) and evaporated. The residue was taken up in water (50 c.c.) and the minimum quantity of N-sodium hydroxide. This solution was washed with ethyl acetate (50 c.c.) and then covered with ethyl acetate (100 c.c.). When the aqueous layer was acidified to Congo-red, there was immediate precipitation of the very insoluble *toluene*-p-*sulphonyl-αγ-L-glutamyldi(glycine* cyclo*hexylamide)* (0·378 g.), which was purified by repeated washing in suspension in sodium hydrogen carbonate solution, water, and ethanol and had m. p. 211—214° (Found: C, 58·0; H, 7·3; N, 12·2. $C_{34}H_{43}O_6N_5S$ requires C, 58·2; H, 7·5; N, 12·1%). The ethyl acetate layer was separated from the acidic aqueous layer and was kept at 0° overnight, during which time toluene-*p*-sulphonyl-γ-L-glutamylglycine *cyclo*hexylamide (0·401 g.), m. p. 197—199° raised to 198—199° on admixture of authentic material (m. p. 199—200°), crystallised. Evaporation of the ethyl acetate liquor afforded *toluene*-p-*sulphonyl-α-L-glutamylglycine* cyclo*hexylamide* (2·77 g., 52%), which was recrystallised from aqueous ethanol and had m. p. 157—160°, $[\alpha]_D^{16}$ −7·7° (*c*, 3·6 in dimethylformamide), pK_{MCS} 6·1 (Found: C, 54·8; H, 6·8; N, 9·5. $C_{20}H_{29}O_6N_3S$ requires C, 54·7; H, 6·6; N, 9·6%).

Toluene-p-sulphonyl-γ-L-glutamyl-L-phenylalanine cyclo*Hexylamide.*—A solution of 1-toluene-*p*-sulphonyl-2-oxo-L-pyrrolidine-5-carboxylic acid [15] (VII; X = OH) (0·283 g., 1 mmole), L-phenylalanine *cyclo*hexylamide (0·266 g., 1·1 mmole), and triethylamine (0·14 c.c., 1 mmole) in acetonitrile (2·5 c.c.) was boiled under reflux for 4·5 hr. Next day the solvents were evaporated

[15] Mizutani, *Z. phys. Chem.*, 1925, **116**, 350; Simon and Heilbronner, *Helv. Chim. Acta*, 1955, **38**, 508.

and the residue was dissolved in water (10 c.c.) and 3N-sodium hydroxide (2 c.c.). The solution was washed with ether (2 × 10 c.c.) and then acidified. The precipitated gel was extracted into ethyl acetate (2 × 50 c.c.), which was dried and evaporated. Crystallisation of the residue (0·400 g.) from aqueous ethanol furnished the *dipeptide derivative* (0·241 g., 48%), m. p. 211—212°, pK_{MCS} 5·2 (Found: C, 61·5; H, 6·6; N, 8·1. $C_{27}H_{35}O_6N_3S$ requires C, 61·2; H, 6·7; N, 7·9%).

Acidic Dissociation Constants.—pK_{MCS} refers to the pH recorded at 20° by a Pye glass-electrode and meter of a solution in 75 vol. % aqueous 2-methoxyethanol at the half-neutralisation point. The meter was standardised with an aqueous buffer at pH 4. The values given previously [4] for compounds (II*a*) and (V*a*) were low, owing to an error in standardisation. The present values [6·1—6·2 for the α-glutamyl series (II), 5·3—5·5 for the γ-series (V)] are in the expected region when allowance is made for the acid-weakening effect of the organic solvent.[39]

Infrared Spectra.—These were determined with a Perkin-Elmer model 21 instrument (sodium chloride prism), Nujol mulls being used, unless otherwise stated. Attention was drawn previously [4] to the fact that in a pair of isomeric glutamyl derivatives the carboxylic acid band is, as expected, at a higher frequency in the γ-isomer, which has the more strongly acidic α-carboxylic acid group. The two further pairs of isomers prepared since then conform with this rule, but the correlation is of little value because the difference between a pair of isomers (15—21 cm.$^{-1}$) is less than the variation in frequency with different structures; this variation is doubtless partly due to differences in the hydrogen-bonding of the carboxyl group. Peptide derivatives with a free α-carboxylic acid group had absorption maxima as follows: toluene-*p*-sulphonylglycine (pK_{MCS} 5·3) **1727**, toluene-*p*-sulphonylglycylglycine (pK_{MCS} 5·4) **1733**, toluene-*p*-sulphonyl-γ-L-glutamylglycine *cyclo*hexylamide **1704**, toluene-*p*-sulphonyl-γ-L-glutamyl-L-phenylalanine *cyclo*hexylamide **1739** (and a weak absorption at 1704), benzoyl-γ-DL-glutamylglycine *cyclo*hexylamide **1745**, γ-benzyl hydrogen benzoylglycyl-L-glutamate **1733** and **1745**, γ-benzyl hydrogen toluene-*p*-sulphonylglycylglycyl-L-glutamate **1736** and **1754**, γ-benzyl hydrogen toluene-*p*-sulphonylglycyl-L-phenylalanyl-L-glutamate **1730** (broad band), toluene-*p*-sulphonylglycyl-L-phenylalanyl-γ-L-glutamylglycine *cyclo*hexylamide **1733** cm.$^{-1}$. Peptide derivatives with a free γ-carboxylic acid group had the following absorption maxima: toluene-*p*-sulphonyl-α-L-glutamylglycine *cyclo*hexylamide **1686**, benzoyl-α-DL-glutamylglycine *cyclo*hexylamide **1730**, benzoylglycyl-α-L-glutamylmorpholine **1739**, toluene-*p*-sulphonylglycylglycyl-α-L-glutamyl-L-phenylalanine *cyclo*hexylamide **1739**, toluene-*p*-sulphonylglycyl-L-phenylalanyl-α-L-glutamylglycine *cyclo*hexylamide **1712** (and a weak absorption at **1692**) cm.$^{-1}$.

Benzoyl-DL-glutamoylglycine *cyclo*hexylamide had maxima at **654, 677, 693, 717, 745, 775, 798, 862, 896, 905, 924, 928, 948, 962, 1007, 1028, 1060, 1079, 1100, 1156, 1172, 1229, 1250, 1277, 1332, 1359, 1416, 1495, 1550, 1587, 1613, 1642, 1681, 1742** cm.$^{-1}$. Toluene-*p*-sulphonylglycyl-L-phenylalanyl-L-glutamoylglycine *cyclo*hexylamide had maxima at **701, 732** (very broad band), **785, 813, 818, 860, 895, 918, 961, 984, 1008, 1056, 1091, 1105, 1163, 1172, 1242, 1252, 1332, 1359, 1399, 1553, 1647, 1704, 1742** cm.$^{-1}$. 1-Methyl-2 : 6-dioxopiperidine in liquid film had maxima at **658, 694, 883, 925, 1044, 1111, 1156, 1199, 1292, 1328, 1357, 1414, 1464, 1675, 1730** cm.$^{-1}$. The neutral product from cyclisation of toluene-*p*-sulphonylglycylglycyl-α-L-glutamyl-L-phenylalanine *cyclo*hexylamide (probably I*c*) in a potassium bromide disc gave a poorly resolved spectrum with maxima at **662, 699, 744, 815, 842, 890, 1030, 1094, 1159, 1250, 1328, 1403, 1453, 1546, 1647** cm.$^{-1}$.

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77. *Reactions of N-Carboxy-α-amino-acid Anhydrides catalysed by Tertiary Bases.*

By D. G. H. Ballard and C. H. Bamford.

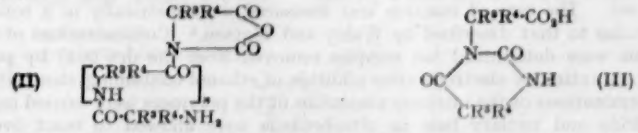
The kinetics of polymerisation of *N*-carboxy-DL-phenylalanine anhydride catalysed by tri-*n*-butylamine are consistent with a reaction mechanism similar to that already proposed for initiation by salts of weak carboxylic acids : bifunctional intermediates with terminal anhydride and basic groups are formed, and enter into coupling reactions. The main difference between the two systems appears to be catalysis of the coupling reaction by tertiary base.

Possible reactions which limit the degree of polymerisation are discussed.

In previous papers [1] we described investigations of the mechanism of polymerisation of *N*-carboxy-α-amino-acid anhydrides (I) when primary or secondary bases or salts are used as initiators. The reactions appear to differ significantly with the two classes of initiator, as regards both mechanism and products. The main process occurring with primary or secondary bases is the normal propagation reaction involving terminal base groups :

(I) NHR^1R^2 + $CR^3R^4(CO)NR^4(CO)O$ → $CR^3R^4(CO{\cdot}NR^1R^2)NHR^5$ + CO_2 . . . . . (1)

and the products are linear polypeptides. Initiation by salts, which is confined to those *N*-carboxy-anhydrides having unsubstituted NH groups, leads to bifunctional intermediates of the type (II) :



(II) $[CR^3R^4(CO)NH]_n CO{\cdot}CR^3R^4{\cdot}NH_2$ (III)

which, by virtue of their free basic groups, participate in reactions with *N*-carboxy-anhydride molecules similar to (I), or enter into a different type of polymerisation process involving the terminal anhydride resides.[1d] Kinetic analysis has shown that coupling of the bifunctional intermediates is one of the most important reactions in the polymerisation. Cyclisation of (II ; $n = 0$) in which the amino-group reacts with the amide carbonyl group yields derivatives of 3-hydantoinylacetic acid (III), which under certain conditions may be a major product.[1c] An alternative cyclisation ($n > 1$) involving the other carbonyl group produces cyclic polypeptides, of which some of the lower members (*e.g.*, cyclic hexaglycine) have been obtained crystalline. It is possible that other chain-breaking reactions occur which lead to linear, and not cyclic, polypeptides.[1d]

In this paper we discuss the reactions initiated by tertiary bases. The polymerisation of *N*-carboxy-anhydrides in the presence of tertiary bases, especially pyridine, is a well-known method of preparing polypeptides. There is great confusion in the literature about the reactivity of *N*-carboxy-anhydrides to tertiary bases. Wessely,[2] who first observed the pyridine-catalysed reaction, reported that other tertiary bases (*e.g.*, trimethylamine) are inactive. Ballard, Bamford, and Weymouth [1c] showed, however, that anhydrides which are not *N*-substituted react readily with other tertiary amines in polar media, yielding cyclic peptides (excluding dioxopiperazines) and derivatives of 3-hydantoinylacetic acid. There has also been controversy as to whether traces of water are necessary for these reactions.[3] For *N*-substituted carboxy-anhydrides Ballard, Bamford, and Weymouth [1c] showed that no reaction occurs between the sublimed anhydrides and purified

[1] (*a*) Ballard and Bamford, *Proc. Roy. Soc.*, 1954, *A*, **223**, 495; Ballard, Bamford, and Weymouth, (*b*) *Nature*, 1954, **174**, 173; (*c*) *Proc. Roy. Soc.*, 1954, *A*, **227**, 155; (*d*) Ballard and Bamford, *Chem. Soc. Sp. Publ. No.* 2, 1955, p. 25.

[2] Wessely, *Z. physiol. Chem.*, 1925, **146**, 72.

[3] Cf., *e.g.*, Hanby, Waley, and Watson, *J.*, 1950, 3009; Coleman, *J.*, 1950, **3222**.

tertiary bases, even in polar media. These results conflict with those of Bilek, Derkosch, Michl, and Wessely,[4] but we believe that their systems contained initiating impurites; although the pyridine used was carefully dried, the anhydrides were not sublimed and the manipulation was not carried out under conditions which precluded the presence of water; for a fuller discussion of this matter see Ballard and Bamford.[1d] As a result of many experiments in which the reagents have been purified with the utmost care we conclude that only those anhydrides with an unsubstituted NH group react at an appreciable rate with tertiary bases. The rate of reaction in these cases is sensitive to the nature of the medium, being higher in polar liquids. There seem to be no grounds for believing that traces of water are necessary for reaction, nor is there any essential difference between pyridine and other tertiary bases. The *N*-substituted anhydrides, if they react at all, do so only extremely slowly by comparison.

A kinetic investigation of the reaction between *N*-carboxy-DL-phenylalanine anhydride and tri-*n*-butylamine in nitrobenzene is described below.

Experimental

Purification of Materials.—*N*-Carboxy-DL-phenylalanine anhydride, prepared by the general methods described by Hanby, Waley, and Watson,[3] was purified by recrystallisation from ethyl acetate–benzene until free from chloride. Immediately before use it was sublimed at $<10^{-3}$ mm.

Tri-*n*-butylamine, from the Eastman-Kodak Corp., was fractionated, kept over barium oxide for at least 48 hr., and distilled in a vacuum.

Nitrobenzene was treated with phosphoric oxide overnight, decanted, treated with barium oxide, and distilled. It was then kept overnight over barium oxide and again distilled.

Methods.—The sealed vessels containing the purified reagents were introduced into a dry box, in which all the subsequent manipulations necessary for preparing the reaction mixture were carried out. The rate of reaction was measured manometrically in a constant-volume apparatus, similar to that described by Waley and Watson.[5] Concentrations of tertiary base in nitrobenzene were determined (on samples removed from the dry-box) by potentiometric titration with an antimony electrode after addition of ethanol containing about 5% of water.[1a]

Some determinations of the intrinsic viscosities of the polymers were carried out. Mixtures of the anhydride and tertiary base in nitrobenzene were allowed to react overnight; the polymers were then precipitated by addition of ether, washed with ether, and dried in a vacuum. Their intrinsic viscosities were measured in dichloroacetic acid.

Results and Discussion

Kinetics.—Fig. 1 shows typical conversion–time curves which indicate that at the lower base concentrations the reaction ceases before the anhydride has reacted completely. This is to be attributed to the formation of the substituted 3-hydantoinylacetic acid, which is a strong acid and neutralises the initiating base. At higher base concentrations the conversion is complete. Titration shows that the yield of acid is quite small, corresponding to about 2% of the anhydride. However, in order to avoid complications due to acid formation we have measured only intial rates of reaction.

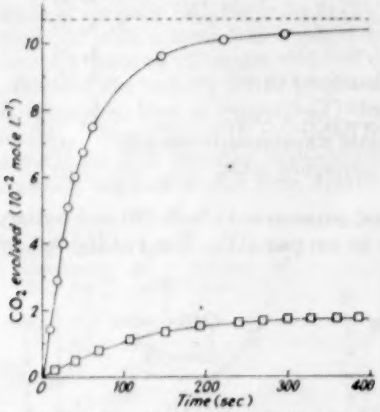
Fig. 2 shows the dependence of the initial rate of reaction on the initial concentration of anhydride $[M]_0$, for different concentrations of (total) base $[T]_0$, at 25°. The order with respect to $[M]_0$ is evidently somewhat greater than one. Similar results were obtained at 15°. The dependence of rate on base concentration at constant $[M]_0$ is shown in Fig. 3 for 25° and 15°. In both cases the overall order in base concentration is slightly less than one. It will be clear from Fig. 3 that the reaction has a small positive temperature coefficient.

The intrinsic viscosities of the resulting poly-DL-phenylalanine measured in dichloroacetic acid are plotted in Fig. 4 against the ratio $[M]_0/[T]_0$. The results show that comparatively high degrees of polymerisation are reached (see p. 386). Further, the overall reactions leading to these high polymers are quite rapid. For example, with $[M]_0 = 1{\cdot}04$ mole l.$^{-1}$ and $[M]_0/[T]_0 = 45$, the reaction is practically complete in ½ hr. and

[4] Bilek, Derkosch, Michl, and Wessely, *Monatsh.*, 1953, **84**, 717.
[5] Waley and Watson, *Proc. Roy. Soc.*, 1949, *A*, **199**, 499.

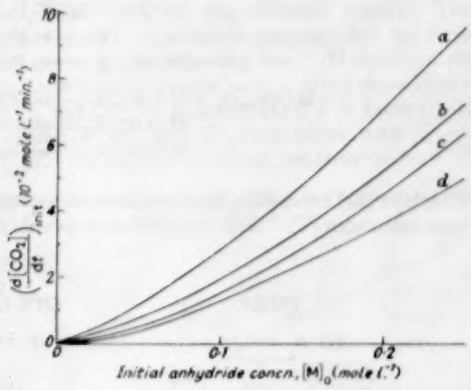
the intrinsic viscosity of the final polymer is 16, corresponding to a degree of polymerisation close to 320. The velocity coefficient [1a] of the normal propagation reaction (1) is $1{\cdot}56 \times 10^{-2}$ mole^{-1} l. sec.$^{-1}$ at 25°, so that in ½ hr. the maximum degree of polymerisation

FIG. 1. *Conversion–time curves for reaction of* N-carboxy-DL-phenylalanine *anhydride with tri-*n*-butylamine in nitrobenzene at 25°; $[M]_0 = 0{\cdot}107$ mole/l.$^{-1}$.*



○ $[T]_0$ (initial total base concn.) = 0·103 mole l.$^{-1}$;
□ $[T]_0 = 1{\cdot}6 \times 10^{-3}$ mole l.$^{-1}$.
Broken line corresponds to 1 mol. of CO_2.

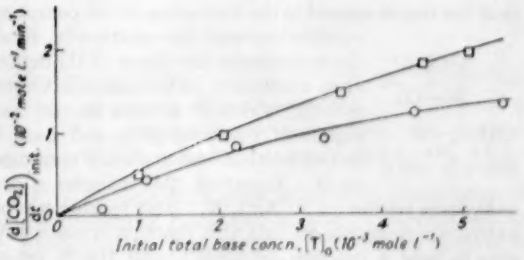
FIG. 2. *Dependence of initial rate of reaction on* N-carboxy-DL-phenylalanine *anhydride concentration* [M]*, for different initial base concentrations,* $[T]_0$*, in nitrobenzene at 25°.*



(*a*) $[T]_0$ 8·1, (*b*) 5·0, (*c*) 4·0, (*d*) $3{\cdot}2 \times 10^{-3}$ mole l.$^{-1}$.

FIG. 3. *Dependence of initial rate of reaction on tri-*n*-butylamine concentration for* $[M]_0 = 0{\cdot}104$ *mole l.*$^{-1}$*, in nitrobenzene.*

□ At 25°.
○ At 15°.



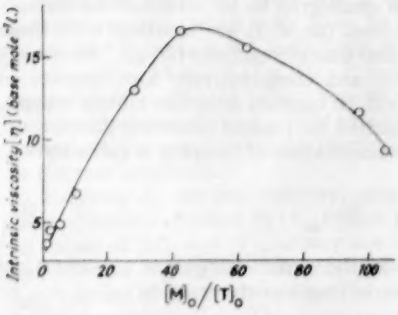


FIG. 4. *Intrinsic viscosities of polymers prepared in nitrobenzene at 25° as a function of* $[M]_0/[T]_0$.

$[M]_0 = 1{\cdot}04$ mole l.$^{-1}$ in all cases.

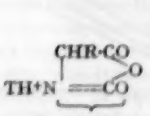
obtainable by this reaction is $1{\cdot}56 \times 10^{-2} \times 1{\cdot}04 \times 1800 = 29$ ($[M]_0$ being assumed to be constant). Clearly the situation is similar to that described for initiation by salts of weak acids, the combination of high rate and high degree of polymerisation being

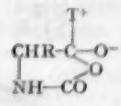
inexplicable in terms of the normal propagation reaction above. Any proposed mechanism must account not only for this fact and the kinetic behaviour of the reaction, but also for the facts that (*a*) *N*-substituted anhydrides do not react, (*b*) dioxopiperazines are not formed, and (*c*) substituted 3-hydantoinylacetic acid derivatives are formed.

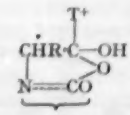
The following mechanism, which is similar to that proposed for initiation by salts of weak acids, is consistent with all the observations:

$$\left.\begin{array}{rcll}
M + T & \rightleftharpoons & C & K\ (a) \\
C + M & \rightleftharpoons & D + T & k_1, k_2\ (b) \\
D & \longrightarrow & M\cdot[AR]_1\cdot X + CO_2 & k_3\ (c) \\
C + M\cdot[AR]_n\cdot X & \longrightarrow & M\cdot[AR]_{n+1}\cdot X + CO_2 + T & k_4\ (d) \\
M\cdot[AR]_m\cdot X + M\cdot[AR]_n\cdot X & \xrightarrow{T} & M\cdot[AR]_{m+n+1}\cdot X + CO_2 & k_5\ (e) \\
M\cdot[AR]_1\cdot X & \longrightarrow & \text{Substituted 3-hydantoinylacetic acid} & (f) \\
M\cdot[AR]_n\cdot X & \longrightarrow & \text{Cyclic polypeptide} + CO_2 & (g)
\end{array}\right\} (2)$$

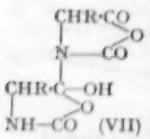
Reaction (2*a*) represents the formation of a complex C between anhydride (M) and tertiary base molecules (T). This complex may possibly be an ion pair (IV; R = $PhCH_2$) but we


(IV)


(V)


(VI)

think that it is more likely to be (V) or (VI) resulting from addition to the acid carbonyl group. It does not seem possible to obtain a satisfactory mechanism on the assumption that the ring is opened in the formation of the complex. The complex is considered to be in equilibrium with the reactants. Reaction between the complex and anhydride produces the dimer (VII) denoted in equation (2*b*) by D. The latter then eliminates carbon dioxide to give the bifunctional intermediate (II; $n = 0$), which is written in (2*c*) as $M\cdot[AR]_1\cdot X$. In this symbols M, X represent the anhydride and base termination respectively, and $[AR]_1$ indicates that the molecule contains one amino-acid residue in addition to M. Equation (2*d*) includes a reaction between the complex and the anhydride residue of $M\cdot[AR]_n\cdot X$. This residue is probably more reactive than the isolated anhydride molecule, so that this reaction is necessary in view of (2*b*). Reaction (2*d*) may also include a reaction between C and the X group of $M\cdot[AR]_n\cdot X$. Coupling between bifunctional intermediates is shown in (2*e*) and is considered to be catalysed by tertiary base. With the exception of this catalysis, reactions (2*c*, *d*, *e*) are identical with those postulated in the case of salt initiation. This is also true of reactions (2*f*, *g*). Since only low yields of hydantoin derivatives are formed, and comparatively high degrees of polymerisation may be attained reactions (2*f*, *g*) will be omitted from the kinetic scheme. The normal propagation reaction has also been omitted for reasons described above.


(VII)

Under our conditions $[M]_0 \gg [T]_0$, hence the concentration of complex is given by

$$[C] = K[M]_0[T] = \frac{K[M]_0[T]_0}{1 + K[M]_0} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

[T] being the concentration of free tertiary base. Applying stationary state considerations to [D] and $\Sigma_n(M\cdot[AR]_n\cdot X)$ (= [X]) we have in the early stages of the reaction:

$$d[D]/dt = k_1[C][M]_0 - k_2[D][T] - k_3[D] = 0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$d[X]/dt = k_3[D] - k_5[T][X]^2 = 0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Also

$$d[CO_2]/dt = k_3[D] + k_4[C][X] + k_5[T][X]^2$$

which, by (3), (4), (5) becomes

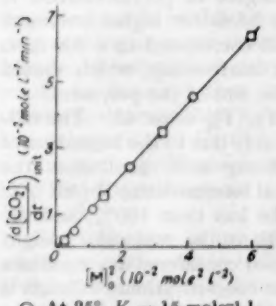
$$\frac{d[CO_2]}{dt} = 2Kk_1[M]_0^2\frac{[T]}{\alpha[T]+1} + K^{\frac{1}{2}}\left(\frac{k_1}{k_5}\right)^{\frac{1}{2}}k_4[M]_0^2\frac{[T]}{(\alpha[T]+1)^{\frac{1}{2}}} \quad \ldots\ldots\ldots (6)$$

$$= 2Kk_1[M]_0^2\frac{[T]_0}{\alpha[T]_0+K[M]_0+1} + K^{\frac{1}{2}}\left(\frac{k_1}{k_5}\right)^{\frac{1}{2}}k_4[M]_0^2\frac{[T]_0}{(\alpha[T]_0+K[M]_0+1)^{\frac{1}{2}}} \quad . \quad (7)$$

where $\alpha = k_2/k_3$.

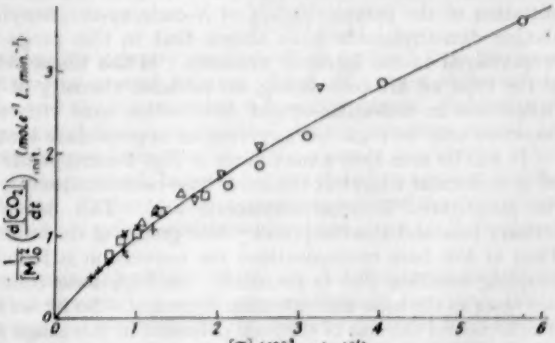
According to equation (7), at constant $[T]_0$ the order in $[M]_0$ lies between one and two, while at constant $[M]_0$ the order in $[T]_0$ is below one. Thus this mechanism leads to a rate equation with a form which might be compatible with the experimental results. The complex form of (7) makes detailed comparison with experiment difficult, but we have examined the validity of the proposed mechanism in the following way. If equation (6) is applicable, then at constant [T] the rate should show simple second-order dependence on $[M]_0$. Now [T] can be calculated from $[T]_0$ and $[M]_0$ by equation (3) if K is known. If a value for K is assumed, corresponding values of $[M]_0$ and $[T]_0$ compatible with [T] = constant can be obtained from equation (3) and the rates of reaction can then be read off

FIG. 5. *Initial rate of reaction in nitrobenzene as a function of* $[M]_0^2$ *for* $[T] = 10^{-3}$ *mole l.*$^{-1}$.



○ At 25°, $K = 15$ mole^{-1} l.
□ At 15°, $K = 25$ mole^{-1} l.

FIG. 6. *Dependence of* $(d[CO_2]/dt)_{initial}/[M]_0^2$ *on* [T]; *nitrobenzene solution at 25°.*



Values of T_0 (10^{-3} mole l.$^{-1}$):

○ 10, ▽ 8·1, △ 5·0, × 4·0, □ 3·2, + 2·1.

from Figs. 2 and 3. It appears that if $K = 15$ mole^{-1} l. a very satisfactory linear relation between rate and $[M]_0^2$ is obtained under conditions calculated to give [T] = constant at 25°. This is shown in Fig. 5 for $[T] = 10^{-3}$ mole l.$^{-1}$. This method of choosing a value of K is reasonably sensitive; thus if K is taken as high as 25 mole^{-1} l. the rate–$[M]_0^2$ plot is concave upwards, while with $K = 10$ mole^{-1} l. it is concave downwards. Use of other values for [T] leads to the same value of K. A similar procedure applied to the results for 15° gives $K = 25$ mol.$^{-1}$ (Fig. 5). It is obviously satisfactory that K should have a negative temperature coefficient, since the forward reaction in the equilibrium (2*a*) would be expected to be exothermic. The rate–$[M]_0^2$ plots for the two temperatures are practically coincident, the negative temperature coefficient of K balancing the positive coefficients due to the rate constants.

Knowing K, we can examine equation (6) further. According to this equation the rates of reaction divided by $[M]_0^2$ when plotted against [T] should lead to a single curve, for all values of $[M]_0$ and $[T]_0$, at any one temperature. This is in fact the case both for 25° and 15° (see Fig. 6). It turns out that by a suitable choice of the parameters α, k_1, $k_4k_5^{-\frac{1}{2}}$, either of the two terms on the right of equation (6) can be made to fit the curve in Fig. 6 satisfactorily. This is not surprising since the terms are not very different in form, but it prevents an unambiguous decision as to their relative magnitudes. Some information about the values of the parameters may, however, be obtained. It follows from equation (6) that if the first term only is used for fitting the curve of Fig. 6 a minimum

value of α is obtained, while use of the second term alone gives a maximum. It may be shown that the values of k_1 and $k_4(k_1/k_5)^{\frac{1}{2}}$ obtained by the use of equation (7) with the extremes of α are maximum values. The limiting values of the parameters obtained in this way are given in the Table. Numerical calculations show that any combination of the

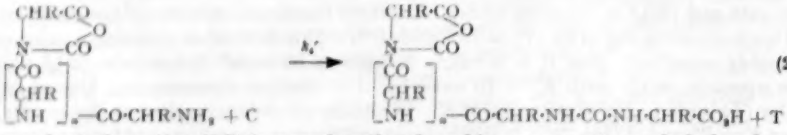
Temp.	K (mole^{-1} l.)	α (mole^{-1} l.) max.	α (mole^{-1} l.) min.	k_1 (mole^{-1} l. sec.$^{-1}$) max.	$k_4(k_1/k_5)^{\frac{1}{2}}$ (mol.$^{-\frac{1}{2}}$ l.$^{\frac{1}{2}}$ sec.$^{-1}$) max.
25°	15	478	148	0·64	0·35
15	25	189	83	0·38	0·15

two terms on the right of equation (7) will fit the experimental results satisfactorily provided the values of the parameters used lie within the range specified in the Table The proposed mechanism is therefore satisfactory kinetically.

The upper limits of k_1 given in the Table are quite close to the values of the corresponding constant deduced for initiation by sodium β-phenylpropionate.[1d] This may imply that the complexes in the two cases have reactivities of the same order, although it must be remembered that the figures tabulated represent maximum values. It is not possible from the results in the Table to estimate the magnitude of $k_4k_5^{-\frac{1}{2}}$.

Molecular Weights.—We now discuss the results shown in Fig. 4. Determinations of the intrinsic viscosities of low polymers (degree of polymerisation <50) prepared by direct initiation of the polymerisation of *N*-carboxy-DL-phenylalanine anhydride by DL-phenylalanine dimethylamide have shown that in this range the degree of polymerisation is proportional to the intrinsic viscosity. If this linear relation holds for higher polymers of the type we are considering, an intrinsic viscosity of 10 will correspond to a 200-mer. Differences in molecular-weight distribution may vitiate this relationship, which should therefore only be regarded as giving an approximate idea of the size of the polymers.

It will be seen that a maximum in Fig. 4 corresponds to $[M]_0/[T]_0 = ca.\ 45$. The fall-off in molecular weight at the lower base concentrations is probably due to the formation of the substituted 3-hydantoinylacetic acid. This, being a strong acid, neutralises the tertiary base and also the primary base groups of the bifunctional intermediates $M{\cdot}[AR]_n{\cdot}X$. Thus at low base concentrations the conversion is found to be less than 100%, and the coupling reaction (2*e*) is retarded. At high base concentrations the molecular weight increases as the base concentration decreases. So far we have not considered any reactions which control the size of the final polymers in this range of base concentrations. Clearly a reaction must occur which effectively destroys one or both of the end groups of the intermediates $M{\cdot}[AR]_n{\cdot}X$ otherwise unlimited coupling could occur. One such reaction could be (2*d'*) similar to (2*d*), but with the X group of $M{\cdot}[AR]_n{\cdot}X$ adding to the amide carbonyl group of the complex C :

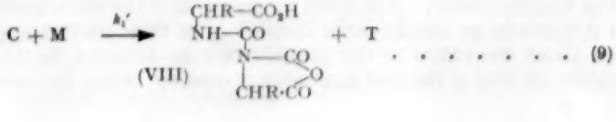


(2*d'*)

The product of reaction (2*d'*) is monofunctional, and hence can act as a chain-breaker. The instantaneous mean degree of polymerisation $\overline{P}_{inst.}$ is readily calculated for the experimentally important case in which the chains are long. It is given by :

$$\overline{P}_{inst.} = \frac{2k_4}{k_4'} + \frac{4(k_1k_4)^{\frac{1}{2}}(1 + K[M])^{\frac{1}{2}}}{K^{\frac{1}{2}}k_4'(\alpha[T]_0 + K[M] + 1)^{\frac{1}{2}}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

Further reactions which could limit the degree of polymerisation are " wrong way " additions of C to M, or C to C, producing monofunctional molecules (VIII) in both cases, *e.g.* :



(9)

The anhydride residue of the compound (VIII) can react with the basic end of M·[AR]$_n$·X and hence form a monofunctional molecule. If reaction (9) proceeds at a rate k_1'[C][M] = Kk_1'[M]^2[T], the instantaneous degree of polymerisation for long chains [governed solely by reaction (9)] is given by :

$$\bar{P}_{inst.} = \frac{4k_3(1 + K[M])}{k_1'(\alpha[T]_0 + K[M] + 1)} + \frac{2K^{\frac{1}{2}}(k_1/k_3)^{\frac{1}{2}}k_3(1 + K[M])^{\frac{1}{2}}}{k_1'(\alpha[T]_0 + K[M] + 1)^{\frac{1}{2}}} \quad . \quad . \quad . \quad . \quad (10)$$

If reaction (9) involves two C molecules (velocity coefficient k_1'') instead of C and M, $\bar{P}_{inst.}$ will be given by an equation derived from (10) by replacing k_1' by $k_1''K[T]_0/(1 + K[M])$.

All three mechanisms predict that $\bar{P}_{inst.}$ should increase as $[T]_0$ decreases at constant [M], and are therefore in qualitative agreement with experiment. We may note that the C–C reaction leads to the strongest dependence of $\bar{P}_{inst.}$ on $[T]_0$, and reaction (2*d'*) to the weakest. In view of the obvious uncertainties we do not consider it worth while pursuing the quantitative implications of these termination mechanisms at present.

Other Reaction Mechanisms.—Wieland [6] suggested a mechanism for the interaction of tertiary bases and *N*-carboxy-anhydrides according to which the anhydride reacts in the ionic forms :

$$\begin{matrix} CHR\cdot CO\cdot T^+ \\ | \\ NH\cdot CO\cdot O^- \end{matrix} \qquad \text{and} \qquad \begin{matrix} CHR\cdot CO\cdot O^- \\ | \\ NH\cdot CO\cdot T^+ \end{matrix}$$

Any mechanism of this type in which the primary reaction of the tertiary base produces ring opening appears unsatisfactory for several reasons. First, it cannot differentiate between *N*-substituted anhydrides and those containing a free NH group. Secondly, it would be expected that large yields of the corresponding dioxopiperazines would be obtained, whereas these substances are not formed at all in the absence of water or other active impurities. Further, the reactions which have to be postulated to account for the nature of the products seem unlikely. Rather similar arguments against the occurrence of Wieland-type reactions in salt-catalysed polymerisations have been given by Ballard and Bamford.[1d]

The difference in behaviour between anhydrides which are *N*-substituted and those which are not seems to indicate that the reaction must proceed through the dimer (VII). If this is admitted it is difficult to produce a mechanism significantly different from that in scheme (2). The apparently high rate of chain growth in these systems is, on this view, mainly accounted for by the coupling reaction (2*e*). This type of mechanism is also satisfactory in that it accounts for the formation of 3-hydantoinylacetic acid derivatives by steps which are chemically reasonable.

The mechanism of polymerisation initiated by tertiary bases is therefore different from that of the reactions brought about by primary or secondary bases. This is understandable if the complex C has the structure (VI). Such a complex is unlikely to be formed with primary or secondary bases; in these cases normal addition to the acid carbonyl group would proceed through the structure (IX), ultimately leading to (X). The protons of the endocyclic NH groups are not involved in this process, and reactions of the type (2*b*) will not occur. In an earlier paper [1a] we have suggested that removal of a proton from the

(IX) $\begin{matrix} {}^+NH_2R' \\ | \\ CHR\cdot C{<}O \\ | \quad\quad O \\ NH{-}CO \end{matrix}$ $\qquad\qquad$ $\begin{matrix} NHR' \\ | \\ CHR\cdot C{-}OH \\ | \quad\quad O \\ NH{-}CO \end{matrix}$ (X)

hydroxyl group of a complex such as (X) facilitates ring opening, since it allows the resonance energy of the peptide group being formed to assist the process. An effect of this kind would be expected to be much less important in the case of (VI) on account of the comparatively low resonance energy of the group $^+T\cdot CO\cdot$. The failure of tertiary bases to produce ring opening in the initial step is therefore not surprising.

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[6] Wieland, *Angew. Chem.*, 1951, **63**, 7; 1954, **66**, 507.

78. *A Novel Method of Cyanoethylation. Part IV.* Substitution Effects.*

By R. J. Bates, J. Cymerman-Craig, M. Moyle, and R. J. Young.

Preparation of *N*-2-cyanoethylarylamines, by amine exchange from 2-diethylaminoethyl cyanide and the arylamine, has been found to depend on the basic strength of the arylamine and to be hindered by *o*-substitution and also by bulky *N*-substituents in the arylamine.

Instead of preformed 2-diethylaminoethyl cyanide, a mixture of vinyl cyanide and diethylamine may be used.

The effect of methyl substitution in the cyanoethyl group itself points to a substitution mechanism. The nature of the amine displaced also affects the yield, diethylamine giving optimum results.

The methiodides of dialkyl-2-cyanoethylamines undergo exchange with cyanide ion to give 1 : 2-dicyanoethane.

It has been shown [1] in Part I that *N*-2-cyanoethylarylamines are obtained by reaction of arylammonium salts with 2-diethylaminoethyl cyanide. Cyanoethylation of a variety of aromatic amines under standard conditions gave the results summarised in Table 1. Two

Table 1.

Arylamine	pK_a (25°)	Yield (%) of *N*-2-cyanoethylarylamine	Yield (%) of recovered arylamine	Arylamine	pK_a (25°)	Yield (%) of *N*-2-cyanoethylarylamine	Yield (%) of recovered arylamine
p-Anisidine	5·29	78	10	*m*-Chloroaniline	3·5	27·5	61
p-Phenetidine	5·25	70	5	2 : 6-Dimethylaniline	3·42	7·6	72·5
p-Toluidine	5·07	67	11	*m*-Acetylaniline	—	0	20
m-Toluidine	4·69	61	15	*p*-Nitroaniline	1·11	0	90
Aniline	4·58	50	19	*N*-Methylaniline	4·85	65	20
o-Anisidine	4·49	42	20	*N*-Ethylaniline	5·11	41	36
o-Toluidine	4·39	25	49	*N*-*n*-Propylaniline	5·02	17·5	40
m-Anisidine	4·20	34	11	*N*-*iso*Propylaniline	—	0·5	95

conclusions emerge from this. The decreasing yield of cyanoethyl derivative as the basic strength of the amine falls is in accord with an S_N2 mechanism of the reaction (1), implying a nucleophilic attack by the arylamine nitrogen on the β-carbon atom of the cyanoethyl group, while the equivalent S_N1 mechanism, with the ionisation of 2-diethylaminoethyl cyanide as rate-determining step, would be expected to give yields independent of the nature of the arylamine.

$$^+NHRR'\cdot CH_2\cdot CH_2\cdot CN + Ar\cdot NH_2 \longrightarrow NHRR' + {}^+NH_2Ar\cdot CH_2\cdot CH_2\cdot CN \quad . \quad . \quad (1)$$

The presence of a substituent *ortho* to the amino-group has already been reported to restrict cyanoethylation by the amine-exchange reaction [2] and by direct cyanoethylation; [3] comparison of the behaviour of *o*-toluidine and 2 : 6-dimethylaniline with that of *m*- and *p*-toluidine further illustrates this *ortho*-effect. Since the effect of lowered basic strength cannot be separated from the steric effect in these cases, several *N*-alkylanilines have been examined. Here the factor is a purely steric one, basicity being comparable throughout, and shows the increasing degree of steric hindrance with increase in size of the *N*-alkyl substituent.

It has been shown in Part III [4] that, whereas vinyl cyanide and *p*-anisidinium chloride did not react at 180°, reaction occurred readily in presence of diethylamine. Application of this method gave an improved yield of *m*-chloro-*N*-2-cyanoethylaniline, and led to the

* Part III, *J.*, 1955, 3628.

[1] Bauer, Cymerman, and Sheldon, Part I, *J.*, 1951, 3311.
[2] Bates and Cymerman-Craig, *J.*, 1954, 1153.
[3] Braunholtz and Mann, *J.*, 1953, 1817.
[4] Cymerman-Craig, Moyle, Nicholson, and Werner, Part III, *J.*, 1955, 3628.

NN'-biscyanoethyl-*o*-phenylenediamine. *p*-Phenylenediamine, from which Braunholtz and Mann [3] obtained only the tetrakiscyanoethyl compound, gave the *NN'*-biscyanoethyl derivative, identified by the presence of a strong >NH band at 3345 cm.$^{-1}$ in its infrared spectrum (Nujol mull).

Attempted acid hydrolysis of *m*-chloro-*N*-2-cyanoethylaniline gave only *m*-chloroaniline; similar elimination of the cyanoethyl group has been reported by Johnson and De Acetis.[5]

The effect of substitution in the cyanoethyl group itself was investigated. *iso*Propenylcyanide did not react with diethylamine under a variety of conditions, but condensed readily with pyrrolidine and piperidine to give 1-2'-cyanopropyl-pyrrolidine and -piperidine respectively. The methiodide of the former underwent amine exchange smoothly with diethylamine to give the previously inaccessible 2-diethylamino-1-methylethyl cyanide.

Of these *iso*propyl cyanides only the first and last condensed satisfactorily with *p*-anisidinium chloride.

The dimethyl-substituted compound, $NEt_2 \cdot CH_2 \cdot CMe_2 \cdot CN$, which is incapable of undergoing an elimination reaction, was prepared by dehydration of 3-diethylamino-2 : 2-dimethylpropionaldoxime. It reacted with *p*-anisidinium chloride, giving only 0·1% of a product, presumably *N*-(2-cyano-2-methylpropyl)-*p*-anisidine, isolated as the unstable alkali-insoluble benzenesulphonamide.

The results agree with the effects predictable for an S_N2 mechanism. Increasing methyl-substitution in the 2-cyanoethyl group results in the carbon sleketon's being related in the same way as in the *n*-propyl, *iso*butyl, and *neo*pentyl group, for which the second-order rate constants [6] (*e.g.*, for the reaction RBr + OEt^- in ethanol at 55°) lie in the order 0·82, 0·03, and 0·0000042, whereas the first-order rate constants for these substituents are of approximately equal magnitude.

Reaction of prop-1-enyl cyanide was also investigated. This condensed smoothly with pyrrolidine giving 1-(2-cyano-1-methylethyl)pyrrolidine, but not with diethylamine. 2-Diethylaminopropyl cyanide was however obtained by an exchange reaction between diethylamine and the pyrrolidine compound. Reaction of these cyanides with *p*-anisidinium chloride gave 40·5 and 50·5% respectively of *N*-(2-cyano-1-methylethyl)-*p*-anisidine. The increased yields compared with those of the isomers suggest that the mechanism of the reaction has changed from S_N2 to S_N1 for the compounds of structure $CN \cdot CH_2 \cdot CHMeR$, which are analogous to secondary alkyl groups such as *iso*propyl or *sec.*-butyl. This change of mechanism is a common phenomenon on passing from the primary to the secondary alkyl series.[7]

The effect of change in the displaced amine was next examined. Reaction of 2-pyrrolidinoethyl cyanide, 2-diethylaminoethyl cyanide, 2-morpholinoethyl cyanide, and *N*-2-cyanoethyl-*N*-ethylbenzylamine with *p*-anisidinium chloride under standard conditions gave the results summarised in Table 2, each experiment being performed in duplicate.

TABLE 2. *Yield of* N-2-*cyanoethyl*-p-*anisidine.*

Starting material	Yield (%)	Recovered arylamine (%)
2-Pyrrolidinoethyl cyanide	26	59
2-Diethylaminoethyl cyanide	78	10
N-2-Cyanoethyl-*N*-ethylbenzylamine	56	30
2-Morpholinoethyl cyanide	45·5	40

The yields of *N*-2-cyanoethyl-*p*-anisidine vary considerably with the amine displaced, passing through a maximum when this is diethylamine. The dependence of the rate of S_N2 reactions on the nature of the displaced group is as yet only imperfectly understood; [8] our results are not explicable in terms of either the volatility or the basic strength of the displaced amine, and it appears likely that two opposing factors are involved. In this

[5] Johnson and De Acetis, *J. Amer. Chem. Soc.*, 1953, **75**, 2766.
[6] Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell, London, 1953, p. 414.
[7] *Idem, op. cit.*, p. 318.
[8] *Idem, op. cit.*, p. 339.

connection it is interesting that Knott [9] reports that Mannich bases with aqueous potassium cyanide form the corresponding nitriles by reaction (2), but that the reaction fails when the group NRR′ is replaced by morpholine, piperidine, or pyrrolidine. We found that compounds of type NC·CH_2·CH_2·NMeRR′}I reacted with aqueous potassium cyanide, forming 1 : 2-dicyanoethane, even when the amine displaced was 4-methylmorpholine or

$$R{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}NRR' + KCN + H_2O \longrightarrow R{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CN + KOH + NHRR' \quad (2)$$

1-methylpyrrolidine. Under the same conditions, 2-hydroxyethyl cyanide gave only 6% of 1 : 2-dicyanoethane; Tsai [10] reports a yield of 22% of succinic acid by hydrolysis during a similar reaction carried out for 4 hours. The conditions used and products obtained suggest either an S_N1 mechanism or fission followed by addition of cyanide ion.

Experimental

Cyanoethylation by 2-Diethylaminoethyl Cyanide.—The arylamine hydrochloride or benzenesulphonate (1 mol.) and 2-diethylaminoethyl cyanide (1·25 mols.) were heated under reflux for 1 hr. at 180°. The cooled melt was treated in either of two ways: (*a*) addition of dry acetone precipitated the diethylammonium salt (70—90%), and the acetone filtrate was fractionally distilled; (*b*) addition of N-sodium hydroxide and extraction with chloroform, followed by fractional distillation of the dried (Na_2SO_4) chloroform extracts. Recovered arylamine in the mixture of arylamine and 2-diethylaminoethyl cyanide was estimated as the acetyl or benzenesulphonyl derivative. Only the isolation of the product is described below in those cases in which the above procedures were used.

N-2-*Cyanoethyl*-N-*methylaniline*. Distillation gave fractions: (*a*) b. p. 46—53°/0·4 mm., n_D^{23} 1·4973, containing 20% of recovered methylaniline; and (*b*) b. p. 127—128°/0·6 mm., $n_D^{23\cdot5}$ 1·5590, *N*-2-cyanoethyl-*N*-methylaniline (65%) (Found: C, 75·3; H, 7·5. Calc. for $C_{10}H_{12}N_2$: C, 75·0; H, 7·55%). The picrate (yellow needles from alcohol) had m. p. 115° (Found: N, 18·2. Calc. for $C_{10}H_{12}N_2,C_6H_3O_7N_3$: N, 18·0%). Whitmore *et al.*[11] give b. p. 175—177°/20 mm., 25% yield, for the base, and m. p. 118° for the picrate, both without analytical figures.

N-2-*Cyanoethyl*-N-*ethylaniline*. Distillation gave fractions: (*a*) b. p. 50—55°/0·4 mm., n_D^{24} 1·5023, containing 36% of recovered *N*-ethylaniline, and (*b*) b. p. 126—127°/0·5 mm., n_D^{24} 1·5505, N-2-*cyanoethyl*-N-*ethylaniline* (41%) (Found: C, 75·9; H, 7·85; N, 15·85. $C_{11}H_{14}N_2$ requires C, 75·95; H, 8·1; N, 16·1%). The *picrate* (yellow needles from alcohol) had m. p. 109—111° (Found: N, 17·65. $C_{11}H_{14}N_2,C_6H_3O_7N_3$ requires N, 17·4%). Reaction with methyl toluene-*p*-sulphonate gave N-2-*cyanoethyl*-N-*ethyl*-N-*methylanilinium toluene*-p-*sulphonate*, needles (from ethyl acetate), m. p. 130—131° (Found: N, 8·1. $C_{19}H_{24}O_3N_2S$ requires N, 7·8%).

N-2-*Cyanoethyl*-N-n-*propylaniline*. Distillation gave fractions: (*a*) b. p. 88—96°/1 mm., n_D^{25} 1·4853, containing 40% of recovered *N*-*n*-propylaniline, and (*b*) b. p. 122—123°/0·5 mm., n_D^{20} 1·5400, N-2-*cyanoethyl*-N-n-*propylaniline* (17·5%) (Found: C, 76·45; H, 8·65; N, 15·15. $C_{12}H_{16}N_2$ requires C, 76·5; H, 8·55; N, 14·9%).

N-iso*Propylaniline*. This base had b. p. 82—85°/0·5 mm., $n_D^{14\cdot5}$ 1·5259, and gave a hygroscopic hydrochloride. N-iso*Propylbenzenesulphonanilide* had m. p. 71—72° (Found: N, 5·2. $C_{15}H_{17}O_2NS$ requires N, 5·1%).

N-2-*Cyanoethyl*-N-iso*propylaniline*. *N-iso*Propylaniline (25·2 g., 0·19 mole) and 2-cyanoethyldiethylmethylammonium iodide (67 g., 0·225 mole) were refluxed for 1 hr. at 180°. Working up as above gave fractions: (*a*) b. p. 60—100°/1 mm., recovered *N-iso*propylaniline (24 g., 95%); (*b*) b. p. 136°/1·5 mm. (0·19 g., 0·5%), *N*-2-cyanoethyl-*N-iso*propylaniline which gave a picrate, m. p. 142°, differing from that of *N-iso*propylaniline (m. p. 87—88°). Lack of material prevented further characterisation.

N-2-*Cyanoethyl*-p-*toluidine*. Working up by method (*b*) gave a distillate, b. p. 48—125°/0·3 mm., containing 11% of recovered *p*-toluidine. The residue crystallised from acetone to give *N*-2-cyanoethyl-*p*-toluidine (67%) as prismatic plates, m. p. 105—106° (Found: C, 75·3; H, 7·55; N, 17·65. Calc. for $C_{10}H_{12}N_2$: C, 75·0; H, 7·5; N, 17·5%). Braunholtz and Mann [12]

[9] Knott, *J.*, 1947, 1190.
[10] Tsai, *J. Amer. Chem. Soc.*, 1951, **73**, 1886.
[11] Whitmore, Mosher, Adams, Taylor, Chapin, Weisel, and Yanko, *J. Amer. Chem. Soc.*, 1944, **66**, 725.
[12] Braunholtz and Mann, *J.*, 1952, 3046.

give m. p. 103—104°. When the products were worked up by method (*a*), dry acetone precipitated a mixture of diethylammonium salt and *N*-2-cyanoethyl-*p*-toluidine. The *hydrochloride* crystallised from alcohol–ether as plates, m. p. 188·5—189·5° (Found : N, 14·6. $C_{10}H_{12}N_2$,HCl requires N, 14·25%).

N-2-*Cyanoethyl*-p-*phenetidine*. Distillation gave fractions: (*a*) b. p. 38—105°/0·6 mm., containing recovered *p*-phenetidine (5%) and (*b*) b. p. 136—138°/ 0·001 mm., N-2-*cyanoethyl*-p-*phenetidine* (70%), crystallising from chloroform–light petroleum (b. p. 40—60°) as plates, m. p. 75—76° (Found : C, 69·8; H, 7·25; N, 14·25. $C_{11}H_{14}ON_2$ requires C, 69·45; H, 7·4; N, 14·7%). The *hydrochloride* crystallised from alcohol–ether as needles, m. p. 136—137° (Found : N, 12·4. $C_{11}H_{14}ON_2$,HCl requires N, 12·4%).

N-2-*Cyanoethyl*-m-*toluidine*. Distillation gave fractions: (*a*) b. p. 46—110°/0·4 mm., containing 15% of recovered *m*-toluidine, and (*b*) b. p. 126—131°/0·4 mm., *N*-2-cyanoethyl-*m*-toluidine (61%), crystallising from chloroform–light petroleum (b. p. 40—60°) as plates, m. p. 47·5—49° (Found : C, 74·8; H, 7·8; N, 17·3. Calc. for $C_{10}H_{12}N_2$: C, 75·0; H, 7·5; N, 17·5%). Braunholtz and Mann [12] give m. p. 47·5—48·5°.

N-2-*Cyanoethyl*-m-*anisidine*. Distillation gave fractions : (*a*) b. p. 58—100°/1 mm., containing 11% of recovered *m*-anisidine, and (*b*) b. p. 180—184°/1 mm., N-2-*cyanoethyl*-m-*anisidine* (34%), crystallising from chloroform–light petroleum (b. p. 40—60°) as needles, m. p. 84—85° (Found : C, 68·0; H, 7·1. $C_{10}H_{12}ON_2$ requires C, 68·15; H, 6·9%).

N-2-*Cyanoethyl*-o-*toluidine*. Distillation gave fractions : (*a*) b. p. 66—71°/1 mm., containing 49% of recovered *o*-toluidine, and (*b*) b. p. 120—121°/0·7 mm., n_D^{23} 1·5530, *N*-2-cyanoethyl-*o*-toluidine (25%) (Found : C, 74·75; H, 7·55; N, 17·2. Calc. for $C_{10}H_{12}N_2$: C, 75·0; H, 7·5; N, 17·5%). Braunholtz and Mann [3] give b. p. 125—126°/0·2 mm. The *picrate* crystallised from methanol as solvated needles, m. p. 205—206° (Found : N, 16·75. $C_{10}H_{12}N_2,C_6H_3O_7N_3,CH_3{\cdot}OH$ requires N, 16·65%); the solvent was removed only at 140° (Found : N, 17·65. $C_{10}H_{12}N_2,C_6H_3O_7$ requires N, 18·0%). The *benzenesulphonate* formed prismatic needles, m. p. 176—177°, from acetone (Found : N, 9·1. $C_{10}H_{12}N_2,C_6H_6O_3S$ requires N, 8·8%).

N-2-*Cyanoethyl*-o-*anisidine*. Distillation gave fractions : (*a*) b. p. 60—81°/0·6 mm., containing 20% of recovered *o*-anisidine, and (*b*) b. p. 165—167°/0·6 mm., n_D^{24} 1·5600, N-2-*cyanoethyl*-o-*anisidine* (42%) (Found : C, 68·3; H, 6·7; N, 16·15. $C_{10}H_{12}ON_2$ requires C, 68·15; H, 6·9; N, 15·9%).

N-2′-*Cyanoethyl*-2 : 6-*dimethylaniline*. Distillation gave fractions: (*a*) b. p. 49—110°/0·5 mm., containing 72·5% of 2 : 6-dimethylaniline, and (*b*) b. p. 122°/0·5 mm., n_D^{16} 1·5400, which solidified on cooling to a low-melting solid (7·6%), N-2′-*cyanoethyl*-2 : 6-*dimethylaniline* (Found : N, 15·95. $C_{11}H_{14}N_2$ requires N, 16·05%). The *benzenesulphonate* formed needles, m. p. 199—200°, from alcohol–ether (Found : C, 61·5; H, 6·1; S, 9·5. $C_{11}H_{14}N_2,C_6H_6O_3S$ requires C, 61·45; H, 6·1; S, 9·6%).

N-2-*Cyanoethyl*-m-*chloroaniline*. (i) A mixture of *m*-chloroanilinium chloride (32·8 g., 0·2 mole) and 2-diethylaminoethyl cyanide (31·5 g., 0·25 mole) was refluxed at 180° for 1·5 hr. Working up by method (*b*) gave fractions (1) b. p. 70—110°/0·5 mm., containing recovered *m*-chloroaniline (61%), and (2) b. p. 152—162°/0·4 mm., n_D^{19} 1·5733 (9·85 g., 27·5%), *N*-2-cyanoethyl-*m*-chloroaniline, solidifying to needles, m. p. 44—47°. An identical experiment at 180° for 1 hr. gave 23% of *N*-2-cyanoethyl-*m*-chloroaniline. Bekhli [13] gives m. p. 48°, b. p. 184—185°/4—5 mm.

Reaction with toluene-*p*-sulphonyl chloride in pyridine gave N-m-*chlorophenyl*-N-2′-*cyanoethyltoluene*-p-*sulphonamide*, needles (from aqueous alcohol), m. p. 95—96° (Found : N, 8·3; S, 9·35. $C_{16}H_{15}O_2N_2SCl$ requires N, 8·35; S, 9·55%).

(ii) *m*-Chloroanilinium chloride (16·4 g., 1 mol.), vinyl cyanide (6·6 g., 1·25 mol.), and diethylamine (9·1 g., 1·25 mols.) were refluxed at 180° for 2·5 hr. Working up by method (*a*) gave fractions: (1) b. p. 70—94°/1·5 mm., containing 7·3 g. (57%) of *m*-chloroaniline and 2·9 g. of *N*-2-cyanoethyldiethylamine, and (2) b. p. 123—128°/0·001 mm., solidifying to needles, m. p. 44—46°, *m*-chloro-*N*-2-cyanoethylaniline (7·6 g., 42·5%).

Attempted Preparation of β-(m-*Chloro*-N-*toluene*-p-*sulphonylanilino*)*propionic Acid*.—*m*-Chloro-*N*-2-cyanoethylaniline (3 g.) and sulphuric acid (70 c.c.; 65% v/v) were refluxed for 2 hr. and the cold mixture was extracted with ether at pH 5. The residue (2·26 g.; m. p. 70—75°) left on evaporation of the dried (Na_2SO_4) ethereal extracts gave, with toluene-*p*-sulphonyl chloride in pyridine, *N*-*m*-chlorophenyltoluene-*p*-sulphonamide, m. p. and mixed m. p. 135—137°.

NN′-*Bis*-2-*cyanoethyl*-o-*phenylenediamine*.—*o*-Phenylenediammonium dibenzenesulphonate

[13] Bekhli, *J. Gen. Chem.* (*U.S.S.R.*), 1951, **21**, 86.

(42·4 g., 1 mol.), diethylamine (18·25 g., 2·5 mols.), and vinyl cyanide (13·25 g., 2·5 mols.) were refluxed at 180° for 2·5 hr. Working up by method (*a*) gave fractions (1) b. p. 58—66°/1·5 mm., n_D^{18} 1·4330, *N*-2-cyanoethyldiethylamine (5·6 g.), and (2) b. p. 190—200°/ 0·001 mm., needles, m. p. 116—118°, *NN'*-bis-2-cyanoethyl-*o*-phenylenediamine (15 g., 70%). Braunholtz and Mann [8] give m. p. 118·5—119°.

NN'-*Bis*-2-*cyanoethyl*-p-*phenylenediamine*.—Repetition of the previous experiment, but with *p*-phenylenediammonium dibenzenesulphonate (42·4 g., 1 mol.), gave *N*-2-cyanoethyldiethylamine (5·8 g.), b. p. 60—66°/1·5 mm., n_D^{19} 1·4340. The residue crystallised from ethanol as plates, m. p. 138—139°, of NN'-*bis*-2-*cyanoethyl*-p-*phenylenediamine* (5 g., 22%) (Found: C, 66·9; H, 6·65. $C_{12}H_{14}N_4$ requires C, 67·2; H, 6·6%). A mixed m. p. with *p*-phenylenediamine was depressed. The substance did not distil even at 260°/0·001 mm. A patent [14] claims m. p. 140°.

2-*Diethylamino*-1 : 1-*dimethylpropionaldehyde*.—*iso*Butyraldehyde (51 g., 0·72 mol.), diethylammonium chloride (63 g., 0·47 mol.), and paraformaldehyde (21·6 g., 0·72 mol.) were refluxed for 1 hr. with vigorous stirring; paraformaldehyde (21·6 g.) and 10N-hydrochloric acid (1 c.c.) were then added, and refluxing and stirring continued for a further hour. After addition of 10N-hydrochloric acid (1 c.c.) the viscous cooled mixture was extracted with cold ethanol (300 c.c.), and the Mannich base hydrochloride obtained on evaporation of the alcoholic extracts was basified and extracted into ether. Distillation of the dried (Na_2SO_4) extracts gave the aldehyde (18·05 g., 68%), b. p. 42—45°/1·5 mm., 38—40°/1 mm., $n_D^{16\cdot5}$ 1·4360 (Found: C, 68·75; H, 11·75; N, 8·95. Calc. for $C_9H_{19}ON$: C, 68·75; H, 12·15; N, 8·95%). The semicarbazone (plates from water) had m. p. 125—126° (Found: C, 56·5; H, 10·35. Calc. for $C_{10}H_{22}ON_4$: C, 56·1; H, 10·35%). Mannich *et al.*[15] give b. p. 175—177° for the aldehyde and m. p. 124—125° for the semicarbazone, neither analyses nor yields being reported. NN-*Diethyl*-N-2'-*formyl*-2'-*methylpropyl*-N-*methylammonium iodide* (needles from ethanol) had m. p. 161—162° (Found: C, 40·35; H, 7·2. $C_{10}H_{22}ONI$ requires C, 40·15; H, 7·4%). The *oxime*, obtained by shaking the aldehyde and hydroxylamine acetate for 6 hr. at pH 10—11, was a mobile oil (45%), b. p. 88—90°/0·6 mm., $n_D^{18\cdot5}$ 1·4659 (Found: C, 62·65; H, 11·7; N, 15·9. $C_9H_{20}ON_2$ requires C, 62·75; H, 11·7; N, 16·25%). The oxime gave a negative test with Schiff's reagent.

2-*Diethylamino*-1 : 1-*dimethylethyl Cyanide*.—The preceding oxime (9 g.) and acetic anhydride (90 g.) were refluxed for 2 hr., and the cooled mixture was basified and extracted with ether. Distillation gave the *cyanide* (6·17 g., 59%), b. p. 56—57°/1 mm., $n_D^{15\cdot5}$ 1·4310 (Found: C, 70·05; H, 11·75; N, 18·0. $C_9H_{18}N_2$ requires C, 70·05; H, 11·75; N, 18·15%). The *methiodide* crystallised from ethanol as needles, m. p. 147—148° (Found: C, 41·05; H, 7·2; N, 8·5. $C_{10}H_{21}N_2I,\frac{1}{2}C_2H_5{\cdot}OH$ requires C, 41·35; H, 7·55; N, 8·75%).

N-(2-*Cyano*-2-*methylpropyl*)-p-*anisidine*.—Reaction of *p*-anisidinium chloride (5·3 g., 1 mol.) and 2-diethylamino-1 : 1-dimethylethyl cyanide (6·4 g., 1·25 mols.) at 180° for 1·5 hr. and working up by method (*a*) gave fractions (1) b. p. 65—130°/3 mm., containing recovered cyanide (3·8 g.) and *p*-anisidine (2·7 g., 66%), and (2) 90—150°/0·001 mm., converted into the benzenesulphonyl derivative. This was washed with aqueous ammonia, sodium hydroxide, hydrochloric acid, and sodium hydrogen carbonate, and the alkali-insoluble derivative (0·03 g., 0·1%) crystallised from aqueous methanol as unstable plates, m. p. 55—57°. Lack of material and the instability of the compound precluded further identification.

1-2'-*Cyanoethylpyrrolidine*.—Obtained from pyrrolidine (10 g., 1 mol.) and vinyl cyanide (10 g., 1·3 mols.) refluxed at 100° for 0·5 hr., this cyanide (15·2 g., 86%) had b. p. 78—80°/2 mm., n_D^{15} 1·4670. Corse *et al.*[16] give 81% after 12 hr. at 100°. N-2-*Cyanoethyl*-N-*methylpyrrolidinium iodide* had m. p. 121—122° (needles from ethanol) (Found: C, 35·9; H, 5·45. $C_8H_{15}N_2I$ requires C, 36·1; H, 5·65%).

4-2'-*Cyanoethyl*-4-*methylmorpholinium Iodide*.—Obtained from 2-morpholinoethyl cyanide,[11] the *methiodide* crystallised from aqueous alcohol as needles, m. p. 178—179° (Found: C, 34·1; H, 5·4. $C_8H_{15}ON_2I$ requires C, 34·05; H, 5·4%).

N-*Ethylbenzylamine*.—Reduction of *N*-acetylbenzylamine by lithium aluminium hydride in boiling ether gave *N*-ethylbenzylamine (60% overall yield from benzylamine), b. p. 62—64°/2 mm., n_D^{14} 1·5180. Parvatiker and McEwen [17] give n_D^{20} 1·5058.

N-*Ethylbenzylammonium chloride* crystallised from ethanol–ether as plates, m. p. 182—183° (Found: C, 63·2; H, 7·9. $C_9H_{13}N,HCl$ requires C, 63·0; H, 8·2%).

[14] Lincoln, Ellis, and Richardson, B.P. 613,807; *Chem. Abs.*, 1949, **43**, 5414.
[15] Mannich, Lesser, and Silten, *Ber.*, 1932, **65**, 378.
[16] Corse, Bryant, and Shenle, *J. Amer. Chem. Soc.*, 1946, **68**, 1911.
[17] Parvatiker and McEwen, *J.*, 1924, 1491.

N-2-*Cyanoethyl*-N-*ethylbenzylamine*.—*N*-Ethylbenzylamine (33·75 g., 1 mol.) and vinyl cyanide (17 g., 1·25 mols.) were refluxed for 10 hr. at 110°. Distillation gave *N*-ethylbenzylamine (10·6 g.), b. p. 68—70°/3 mm., n_D^{16} 1·5170 and N-2-*cyanoethyl*-N-*ethylbenzylamine* (30·2 g., 94% on reacted amine), b. p. 148°/3 mm., n_D^{16} 1·5170 (Found: C, 76·7; H, 8·4. $C_{12}H_{16}N_2$ requires C, 76·5; H, 8·5%). The *methiodide* crystallised from ethanol as needles, m. p. 125—126° (Found: C, 47·4; H, 5·7. $C_{13}H_{19}N_2I$ requires C, 47·31; H, 5·8%).

1-2′-*Cyanopropylpyrrolidine*.—Pyrrolidine (7·2 g., 1 mol.) and *iso*propenyl cyanide (6·7 g., 1 mol.) were refluxed at 110° for 8 hr. Distillation gave unchanged material (1·0 g.), b. p. 38—40°/60 mm., and 1-2′-*cyanopropylpyrrolidine* (12·15 g., 88%), b. p. 132—136°/60 mm., 58°/0·8 mm., n_D^{19} 1·4560 (Found: C, 69·7; H, 10·25. $C_8H_{14}N_2$ requires C, 69·55; H, 10·2%). The *methiodide* crystallised from ethanol–ether as needles, m. p. 100—101° (Found: C, 38·55; H, 6·0. $C_9H_{17}N_2I$ requires C, 38·5; H, 6·1%). Treatment of this methiodide with lithium picrate gave 1-2′-*cyanopropyl*-1-*methylpyrrolidinium picrate* as yellow plates (from ethyl acetate), m. p. 130—131° (Found: C, 47·3; H, 4·9. $C_{15}H_{19}O_7N_5$ requires C, 47·25; H, 5·0%).

1-2′-*Cyanopropylpiperidine*.—Reaction of piperidine (17 g., 0·2 mole) and *iso*propenyl cyanide (10 g., 0·15 mole) at 110° for 10 hr. under reflux gave unchanged material (5 g.), b. p. 80—104°/760 mm., and the new *cyanide* (14·8 g., 72% on reacted cyanide), b. p. 70—72°/2 mm., $n_D^{17\cdot6}$ 1·4662 (Found: C, 71·1; H, 10·25. $C_9H_{16}N_2$ requires C, 71·0; H, 10·55%). The *methiodide* crystallised from ethanol–ether as needles, m. p. 144—145° (Found: C, 40·7; H, 6·35. $C_{10}H_{19}N_2I$ requires C, 40·8; H, 6·5%).

Preparation of 2-*Diethylamino*-1-*methylethyl Cyanide*.—(*A*) Molar quantities of diethylamine and *iso*propenyl cyanide failed to react when refluxed for 5 hr. with or without benzyltrimethylammonium hydroxide or heated at 175° for 2 hr. or at 215° for 3 hr.

(*B*) 1-2′-Cyanopropyl-1-methylpyrrolidinium iodide (44·0 g.) and diethylamine (60·0 g., 5 mols.) were heated at 100° for 8 hr. Ether-extraction of the residue after removal of diethylamine gave 2-*diethylamino*-1-*methylethyl cyanide* (13·2 g., 60%), b. p. 92°/20 mm., n_D^{15} 1·4350 (Found: C, 68·4; H, 11·5. $C_8H_{16}N_2$ requires C, 68·5; H, 11·5%). The *methiodide* crystallised from alcohol–ether as needles, m. p. 166—168° (decomp.) (Found: C, 37·8; H, 6·55. $C_9H_{19}N_2I$ requires C, 38·3; H, 6·8%).

1-(2-*Cyano*-1-*methylethyl*)*pyrrolidine*.—Pyrrolidine (14·2 g., 0·2 mole) and prop-1-enyl cyanide (17 g., 0·2 mole) were refluxed at 130° for 3 hr. Distillation gave the new *cyanide* (24·6 g., 89%), b. p. 121—122°/25 mm., n_D^{25} 1·4660 (Found: C, 69·4; H, 10·3. $C_8H_{14}N_2$ requires C, 69·5; H, 10·2%). The hygroscopic methiodide on treatment with lithium picrate gave *N*-methylpyrrolidinium picrate, crystallising from ethyl acetate as yellow plates, m. p. 222° (lit., m. p. 222°) (Found: C, 42·1; H, 4·5; N, 17·75. Calc. for $C_{11}H_{14}O_7N_4$: C, 42·0; H, 4·5; N, 17·85%).

2-*Diethylaminopropyl Cyanide*.—(*a*) A mixture of 1-(2-cyano-1-methylethyl)-1-methylpyrrolidinium iodide (21·5 g.) and diethylamine (36·5 g., 6 mols.) was refluxed at 100° for 6 hr. Removal of diethylamine and ether-extraction of the residue gave 2-*diethylaminopropyl cyanide* (9·7 g., 91%), b. p. 101—102°/25 mm., n_D^{24} 1·4380 (Found: C, 68·05; H, 11·5. $C_8H_{16}N_2$ requires C, 68·5; H, 11·5%). The *methiodide* crystallised from alcohol as needles, m. p. 172—174° (decomp.) (Found: C, 38·0; H, 6·6. $C_9H_{19}N_2I$ requires C, 38·3; H, 6·8%). (*b*) Prop-1-enyl cyanide was recovered quantitatively after 6 hours' refluxing with diethylamine at 100°.

2-*Methylprop*-1-*enyl Cyanide*.—Decarboxylation of α-cyano-β-methylcrotonic acid[18] in presence of a catalytic amount of copper bronze commenced at 180—190°, giving 2-methylprop-1-enyl cyanide (76%), b. p. 140—143°/760 mm., n_D^{20} 1·4232 (lit., b. p. 140—142°).

Attempted Preparation of 2-*Diethylamino*-2-*methylpropyl Cyanide*.—No reaction occurred between diethylamine and 2-methylprop-1-enyl cyanide even in the presence of benzyltrimethylammonium hydroxide or potassium carbonate.

N-2-*Cyanoethyl*-p-*anisidine*.—This had b. p. 136—145°/0·001 mm., m. p. and mixed m. p. 62—64°. Each of the following experiments was performed in duplicate. (*A*) *N*-2-Cyanoethylpyrrolidine (12·4 g., 1·5 mols.) and *p*-anisidinium chloride (10·65 g., 1 mol.) were refluxed at 180° for 1·5 hr. Working up by method (*b*) gave fractions (1) b. p. 84—100°/1 mm., containing 59% of recovered *p*-anisidine, and (2) *N*-2-cyanoethyl-*p*-anisidine (3 g., 26%). (*B*) *N*-2-Cyanoethylmorpholine (14 g., 1·5 mols.) by the same method afforded fractions (1) b. p. 112°/4 mm. to 120°/0·001 mm., containing 40% of recovered *p*-anisidine, and (2) *N*-2-cyanoethyl-*p*-anisidine (5·3 g., 45·5%). (*C*) *N*-2-Cyanoethyl-*N*-ethylbenzylamine (14·1 g., 1·5 mols.) by the same method

[18] Knoevenagel, G.P. 162,181.

gave fractions (1) b. p. 96—150°/3 mm., containing 30% of *p*-anisidine, and (2) *N*-2-cyanoethyl-*p*-anisidine (4·9 g., 56%). (*D*) Morpholine (9·7 g., 1·5 mols.), vinyl cyanide (5·3 g., 1·5 mols.), and *p*-anisidinium chloride (10·65 g., 1 mol.) were refluxed at 180° for 1·5 hr. Working up by method (*b*) gave fractions: (1) b. p. 94—100°/1 mm., containing 49% of *p*-anisidine and *N*-2-cyanoethylmorpholine(4·3 g.), and (2) *N*-2-cyanoethyl-*p*-anisidine (4·35 g., 37%).

N-2-*Cyanopropyl*-p-*anisidine*.—(*A*) 1-2′-Cyanopropylpyrrolidine (15 g., 1·25 mols.) and *p*-anisidinium chloride (15 g., 1 mol.) were refluxed at 180° for 1·5 hr. Working up by method (*b*) gave fractions (1) b. p. 60°/0·5 mm. to 120°/0·001 mm., containing 80% of *p*-anisidine, and (2) b. p. 120—130°/0·001 mm., converted into the alkali-insoluble N-*benzenesulphonyl*-N-2′-*cyanopropyl*-p-*anisidine* (2·4 g., 8% yield), crystallising from benzene–light petroleum (b. p. 60—90°) as needles, m. p. 56—57° (Found: C, 61·5; H, 5·3. $C_{17}H_{18}O_3N_2S$ requires C, 61·8; H, 5·5%).

(*B*) Repetition of this experiment gave a second form of this *benzenesulphonamide*, crystallising from chloroform–light petroleum as needles, m. p. 91—92° (Found: C, 61·5; H, 5·4%).

(*C*) 1-2′-Cyanopropylpiperidine (12·7 g., 1·25 mols.) and *p*-anisidinium chloride (10·6 g., 1 mol.) were refluxed at 180° for 1·5 hr. Working up by method (*a*) gave piperidinium chloride (7·2 g., 89%), m. p. and mixed m. p. 230—232°. Distillation of the acetone filtrate gave fractions of b. p. 70—98°/0·7 mm. and b. p. 100—130°/0·001 mm.; together these contained 69% of recovered *p*-anisidine. No alkali-insoluble benzenesulphonamide was obtained.

(*D*) 2-Diethylamino-1-methylethyl cyanide (3·5 g.) and *p*-anisidinium chloride (4 g., 1 mol.) were treated as in (*A*) above. Working up gave *p*-anisidine (84%), and a residue which was converted into the alkali-insoluble benzenesulphonamide (0·85 g., 10%), m. p. 88—90°, undepressed on admixture with the product obtained as in (*B*).

N-(2-*Cyano*-1-*methylethyl*)-p-*anisidine*.—(*A*) *p*-Anisidinium chloride (10 g., 1 mol.) and 1-(2-cyano-1-methylethyl)pyrrolidine (10·2 g., 1·25 mols.) were refluxed at 180° for 1·5 hr. Working up by method (*b*) gave fractions (1) b. p. 80—100°/1 mm., containing 20% of *p*-anisidine, (2) b. p. 100—120°/0·001 mm., converted into the benzenesulphonamide [the alkali-soluble portion corresponded to a further 20% of recovered *p*-anisidine; the alkali-insoluble portion (5·5 g., 28%) crystallised from ethanol as needles of N-*benzenesulphonyl*-N-2-*cyano*-1-*methylethyl*-p-*anisidine*, m. p. 81—82° (Found: C, 61·6; H, 5·5. $C_{17}H_{18}O_3N_2S$ requires C, 61·8; H, 5·5%)], and (3) b. p. 122—125°/0·001 mm., needles, m. p. 91—92° (from ethanol), N-(2-*cyano*-1-*methylethyl*)-p-*anisidine* (1·45 g., 12·5%) (Found: C, 69·2; H, 7·4. $C_{11}H_{14}ON_2$ requires C, 69·45; H, 7·4%). (*B*) Reaction of *p*-anisidinium chloride (8 g., 1 mol.) and 2-diethylaminopropyl cyanide (7 g., 1 mol.), as described in (*A*), gave *p*-anisidine (42·5%), b. p. 80—90°/0·5 mm., and *N*-(2-cyano-1-methylethyl)-*p*-anisidine (4·8 g., 50·5%), b. p. 126—132°/0·001 mm., needles, m. p. and mixed m. p. 88—90°.

NN-*Dibenzenesulphonyl*-p-*anisidine*.—Treatment of *p*-anisidine in pyridine with excess of benzenesulphonyl chloride at 100°, and working up with ammonia, sodium hydroxide solution, dilute hydrochloric acid, and sodium hydrogen carbonate solution gave the stable NN-*dibenzenesulphonyl*-p-*anisidine*, crystallising from alcohol as plates, m. p. 139—140° (Found: C, 56·75; H, 4·25; N, 3·3; S, 16·0. $C_{19}H_{17}O_5NS_2$ requires C, 56·55; H, 4·25; N, 3·45; S, 15·9%).

1 : 2-*Dicyanoethane*.—The reactants were added to gently boiling water and refluxed for 35 min.; the cold solution was extracted with chloroform. All experiments were performed in duplicate. All samples of 1 : 2-dicyanoethane had m. p. and mixed m. p. 52—54°.

(*a*) Reaction of 2-cyanoethyldiethylmethylammonium iodide (2·7 g., 1 mol.), potassium cyanide (1·3 g., 2 mols.), and water (5 c.c.) gave 1 : 2-dicyanoethane (0·5 g., 62·5%).

(*b*) Benzyl-2-cyanoethylethylmethylammonium iodide (3·3 g., 1 mol.), potassium cyanide (1·3 g., 2 mols.), and water (5 c.c.) were treated as above. The chloroform extract was washed with 2N-hydrochloric acid. The neutral fraction gave 1 : 2-dicyanoethane (0·45 g., 56%), and the basic fraction gave *N*-ethyl-*N*-methylbenzylamine (0·85 g., 57%) [picrate, m. p. 113—114° (lit., m. p. 113°)].

(*c*) 1-2′-Cyanoethyl-1-methylpyrrolidinium iodide (5·32 g., 1 mol.), potassium cyanide (2·6 g., 2 mols.), and water (10 c.c.) gave 1 : 2-dicyanoethane (0·8 g., 50%).

(*d*) 4-2′-Cyanoethyl-4-methylmorpholinium iodide (16·9 g., 1 mol.), potassium cyanide (7·8 g., 2 mols.), and water (30 c.c.), worked up as in (*b*), gave 1 : 2-dicyanoethane (1·35 g., 28%). The basic portion (3·3 g., 54%) was 4-methylmorpholine (picrate, m. p. 225°; methiodide, m. p. 246°; lit., 225° and 246° respectively).

(*e*) 2-Hydroxyethyl cyanide (2·15 g., 1 mol.), potassium cyanide (3·9 g., 2 mols.), and water (15 c.c.) gave 1 : 2-dicyanoethane (0·15 g., 6%).

Various.—Some additional salts are recorded in Table 3.

TABLE 3. *Arylammonium benzenesulphonates.*

Benzenesulphonate	Formula	M. p.	Found (%) C	Found (%) H	Required (%) C	Required (%) H
p-*Nitroanilinium* [a,b]	$C_6H_9O_5N_2.C_6H_5O_3S$	235—236°	48·9	4·3	48·7	4·1
m-*Acetylanilinium* [a,b]	$C_8H_{12}ON.C_6H_5O_3S$	163—164	57·4	5·0	57·3	5·1
o-*Anisidinium* [d]	$C_7H_{10}ON.C_6H_5O_3S$	200—201	55·5	5·25	55·5	5·35
m-*Anisidinium* [c]	$C_7H_{10}ON.C_6H_5O_3S$ [e]	170—171	—	—	—	—
2 : 6-*Dimethylanilinium* [b]	$C_8H_{12}N.C_6H_5O_3S$ [f]	183—184	—	—	—	—
o-*Phenylenediammonium* [c]	$C_6H_{10}N_2.2C_6H_5O_3S$	245 [a]	50·65	4·65	50·9	4·7
p-*Phenylenediammonium* [c]	$C_6H_{10}N_2.2C_6H_5O_3S$	340—345 [a]	50·75	4·75	50·9	4·7

[a] With decomp. [b] Yellow. [c] From MeOH. [d] From EtOH. [e] From H_2O. [f] Found: N, 5·3. Reqd.: N, 5·0%. [g] Found: N, 4·9; S, 11·5. Reqd.: N, 5·0; S, 11·5%.

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79. 1-*Phenylnaphthalenes. Part III.** *The Effect of Substituents and their Position on the Absorption Spectra of* 1-*Phenylnaphthalene*-2 : 3-*dicarboxylic Anhydrides.*

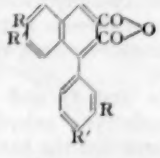
By F. G. BADDAR and ZAKI SAWIRES.

Structures proposed for some alkoxy-1-phenylnaphthalene-2 : 3-dicarboxylic anhydrides are supported by their absorption spectra. Shifts in the absorption bands are observed with the change in the position of the alkoxyl group. The importance of directional effects in connection with the absorption of light is shown.

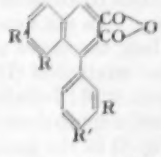
THIS investigation was primarily designed to establish the structure of some di- and tetra-alkoxy-1-phenylnaphthalene-2 : 3-dicarboxylic anhydrides, which could not be easily verified by chemical means.[1] The study was then extended to other 1-phenylnaphthalene-2 : 3-dicarboxylic anhydrides previously synthesised by Baddar,[2] and Baddar and El-Assal,[3] in order to correlate their structure with their electronic absorption spectra. The measurements were carried out on a Beckman D.U. spectrophotometer with glacial acetic acid or light petroleum solutions.

Results and Discussion.—The spectrographic results are given in the Table. The spectra of the 6-alkoxy-1-*m*-alkoxyphenylnaphthalene-2 : 3-dicarboxylic anhydrides are

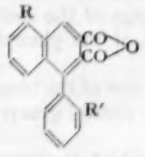
(I*a*) : R = R′ = H
(I*b*) : R = OMe, R′ = H
(I*c*) : R = OEt, R′ = H
(I*d*) : R = OPr^i, R′ = H
(I*e*) : R = R′ = OMe
(I*f*) : R = R′ = OEt
(I*g*) : R = H, R′ = OMe

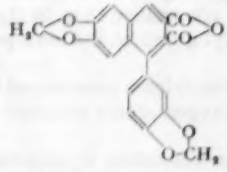


(II*a*) : R = OMe, R′ = H
(II*b*) : R = OEt, R′ = H
(II*c*) : R = OPr^i, R′ = H
(II*d*) : R = R′ = OEt



(III*a*) : R = R′ = OMe
(III*b*) : R = OMe, R′ = H
(III*c*) : R = H, R′ = OMe





(IV)

similar; they differ from those of the 8-alkoxy-1-*m*-alkoxyphenylnaphthalene-2 : 3-dicarboxylic anhydrides (Fig. 1). This is taken to be a good support to the structure

* Part II, *J.*, 1955, 1714.

[1] Baddar, Fahim, and Galaby, *J.*, 1955, 465.
[2] Baddar, *J.*, 1947, 224.
[3] Baddar and El-Assal, *J.*, 1948, 1267; 1951, 1844.

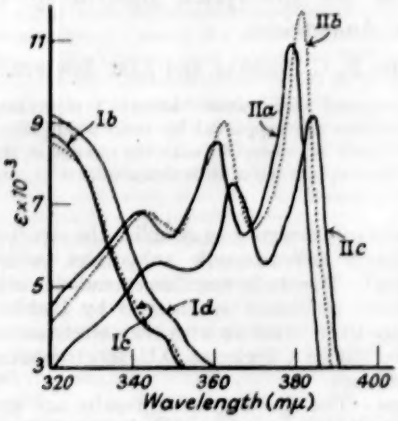
assigned to 6-*iso*propoxy-1-*m*-*iso*propoxyphenylnaphthalene-2 : 3-dicarboxylic anhydride (I*d*) which was not established by chemical means.[1]

The 8-alkoxy-isomers (II*a*, *b*, and *c*) (Fig. 1) show three related maxima, which proves the correctness of the structure assigned to them.[1] The slight bathochromic shift from the methoxy-isomer (II*a*) to the *iso*propoxy-isomer (II*c*) may be attributed to the increase in the electron-repelling character (+*I*) of the alkyl group.

The curves for the 6-alkoxy-compounds (I*b*, *c*, and *d*) have broadly similar features to those of the parent non-substituted anhydride (I*a*) with an all-over increase in intensity and a relatively small shift towards the red (Figs. 2, 3, and 4).

The 8-alkoxy-derivatives (II*a*, *b*, and *c*) (Figs. 2, 3, and 4) and the 5-methoxy-derivatives (III*a* and *b*) (Fig. 5) reveal on comparison with the parent anhydride (I*a*) a bathochromic shift, smaller than that of the 6-alkoxy-isomers, at wavelengths shorter than 290 mμ and a more extended shift for the absorption at longer wavelengths with a minimum at *ca.* 300 mμ, which is not observed in the 6-alkoxy-compounds (Figs. 2, 3, and 4). This difference in absorption is reflected in the colour of these compounds; thus, whereas the 6-alkoxy-derivatives are colourless, the 8- and 5-alkoxy-isomers are yellow.

FIG. 1.



The curve for the yellow 7-methoxy-1-*p*-methoxyphenylnaphthalene-2 : 3-carboxylic anhydride (I*g*) (Fig. 5) is close to those of the 6-alkoxy-anhydrides (I*b*, *c*, and *d*) at wavelengths shorter than 310 mμ. In the near ultraviolet there is a shift towards the red and intensity is also higher; here the curve nearly coincides with a synthetic curve (curve *c*, Fig. 2) for an equimolecular mixture of (II*a* and I*b*).

The curves for the yellow 6 : 7-dialkoxy- (I*e* and *f*) and 6 : 7-methylenedioxy-1-(3 : 4-methylenedioxyphenyl)naphthalene-2 : 3-dicarboxylic anhydride (IV) (Fig. 6) are similar to that for (I*g*) (Fig. 5) in the general features, but the bathochromic shift and the increase in intensity are smaller than in (I*g*) because of the steric inhibition of resonance exerted by the alkoxyl group at the *meta*-position of the phenyl nucleus on that at the *para*-position.[4]

This effect, however, is least pronounced in the case of the bismethylenedioxy-derivative (IV), since the two oxygen atoms attached to the phenyl group are fixed together by the $-CH_2-$ bridge.

The curve for the colourless 7 : 8-diethoxy-1-(3 : 4-diethoxyphenyl)naphthalene-2 : 3-dicarboxylic anhydride (II*d*) (Fig. 6) is in agreement with those for the preceding tetra-alkoxy-compounds (I*e*, I*f*, and IV) in the far ultraviolet only, and with those for the 6-alkoxy-derivatives (I*b*, *c*, and *d*) in the near ultraviolet. This may be the result of inhibition of resonance of the phenyl group as a whole with the naphthalene nucleus, caused by the 8-ethoxyl group.

[4] Burawoy and Chamberlain, *J.*, 1952, 3734.

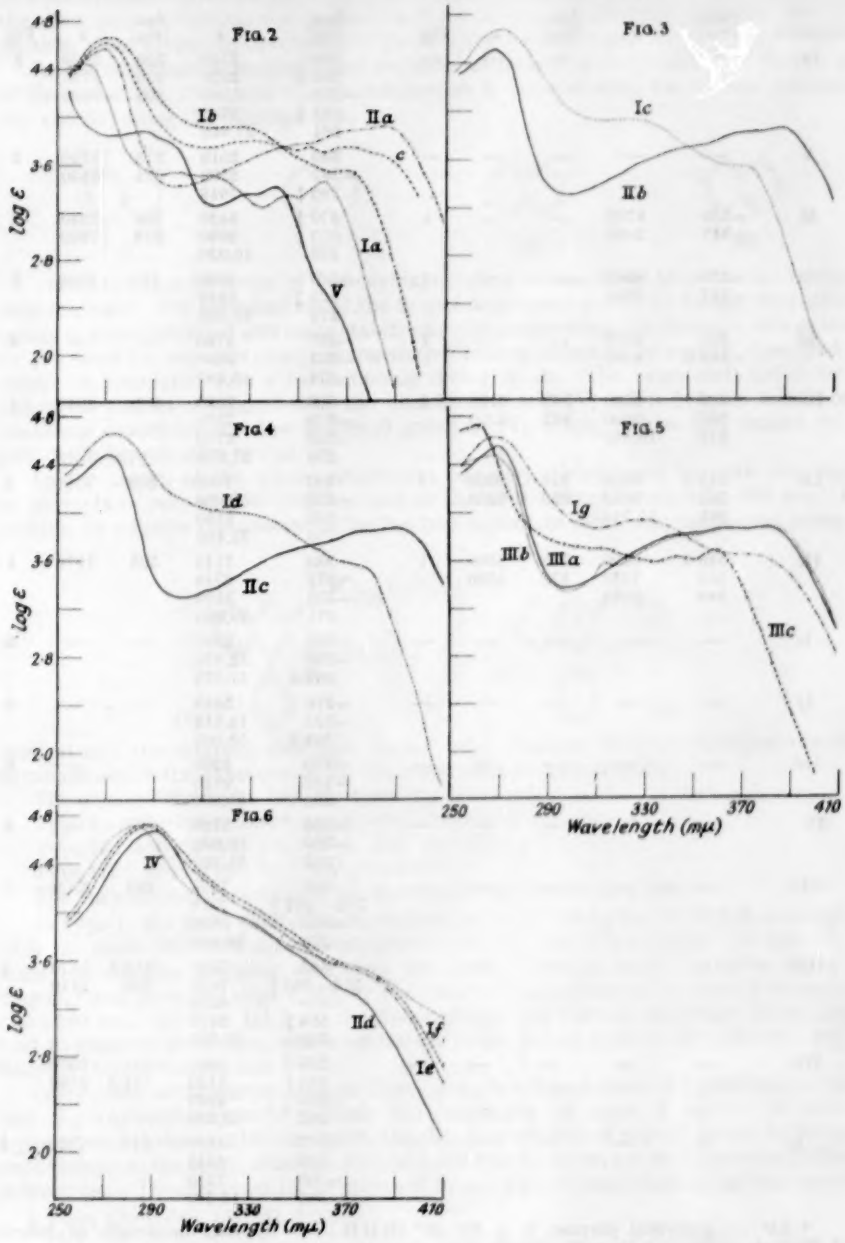


FIG. 2
Ib
IIa
c
Ia
V
FIG. 3
Ic
IIb
FIG. 4
Id
IIc
FIG. 5
Ig
IIIb
IIIa
IIIc
FIG. 6
IV
IId
If
Ie
log ε
4·8
4·4
3·6
2·8
2·0
250
290
330
370
410
Wavelength (mμ)

Compound	Solvent: light petroleum *					Solvent: glacial acetic ("AnalaR")				
	$\lambda_{max.}$ (mμ)	ε	$\lambda_{min.}$ (mμ)	ε	Fig.	$\lambda_{max.}$ (mμ)	ε	$\lambda_{min.}$ (mμ)	ε	Fig.
Ia	—	—	—	—	—	360	2740	350	2070	2
						346·5	2120	336	1710	
						~308	3180	295	3290	
						299 ‡	3380			
						261	27,840			
V	—	—	—	—	—	340	2510	315	1740	2
						~332	2200	271	6450	
						286 ‡	7548			
Ib	~320	8700	—	—	1	370 ‡	3430	364	3340	2
	~347	3830				325 ‡	8060	316	7990	
						270	46,090			
Ic	~320	8500	—	—	1	~367	3580	315	8280	3
	~347	3830				325 ‡	8440			
						273	47,200			
Id	~320	9200	—	—	1	~367	3790	—	—	4
	~348·5	4400				~321	9840			
						274	45,100			
IIa	342	6800	349	6190	1	386	7820	300	2645	2
	360	8550	367	6210		~370	7375			
	378	10,850				~355	5770			
						270	37,070			
IIb	343·5	6820	351	6300	1	387	7100	300	2100	3
	362	9020	369	6350		~375	6650			
	381	11,710				~355	5190			
						270	32,410			
IIc	346·5	5600	355	5380	1	389	7145	303	1970	4
	364	7530	372	5500		~375	6710			
	384	9165				~355	5195			
						271	30,260			
Ie	—	—	—	—	—	~366	3545	—	—	6
						~320	12,870			
						286·5	51,770			
If	—	—	—	—	—	~370	3645	—	—	6
						~320	14,310			
						288·5	52,000			
IId	—	—	—	—	—	~370	2200	—	—	6
						~320	9810			
						290	45,800			
IV	—	—	—	—	—	~366	3720	—	—	6
						~320	10,080			
						283	51,260			
IIIa	—	—	—	—	—	380	7250	298	2300	5
						375—362 †	7070			
						~350	6520			
						270	35,400			
IIIb	—	—	—	—	—	382	7350	318·5	3470	5
						374—365 †	7050	298	2140	
						~350	6220			
						314 ‡	3670			
						270	29,200			
IIIc	—	—	—	—	—	359·5	4660	351	3900	5
						344 ‡	4130	334·5	3760	
						~308	4940			
						262	53,200			
Ig	—	—	—	—	—	~375	4200	310	7250	5
						329	8440			
						~305	7510			
						269	42,280			

* I.P. for analytical purpose, b. p. 60—80° (B.D.H.). ~ Approx. wavelength of inflexion ‡ Poor persistence. † Very close bands of poor persistence.

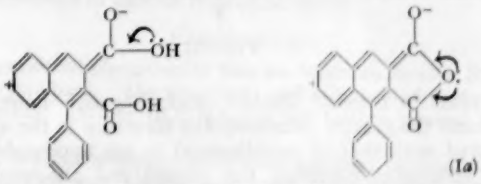
The variations in the absorption of light caused by the introduction of alkoxyl groups in 1-phenylnaphthalene-2 : 3-dicarboxylic anhydride can be understood if we assume that the electronic excitations are parallel to those in the naphthalene molecule, and if we consider these variations in relation to the direction of excitation.[5]

In the naphthalene molecule four extreme structures (i—iv) contribute to the state of the molecule. In (i) and (ii) the polarisation is directed along the vertical axis and in (iii) and (iv) along the diagonal axis.

(i) (ii) (iii) (iv)

The absorption spectrum of 1-phenylnaphthalene is considered to be similar to that of naphthalene.[6] The introduction of the 2- and 3-carboxyl groups in 1-phenylnaphthalene brings in more extended and more stabilised conjugation along the diagonal axis as shown by (V), since the negative charge is transferred from a carbon to an oxygen atom, and this should be associated with a bathochromic shift (Fig. 2). The larger shift noted for the anhydride (I*a*) as compared with the dicarboxylic acid (V) arises because inhibition of resonance caused by the free hydroxyl group in (V) is larger than that caused by the anhydride oxygen atom in (I*a*).

In the curves of the alkoxy-anhydrides one may discriminate between two regions of absorption, *viz.*, at 260—290 mμ and in the near ultraviolet at 360—390 mμ. It is possible to allocate the absorption in the two regions to electronic excitations along the



(V) (I*a*)

vertical and the diagonal direction, respectively. Various workers visualised the effect of orientation of the molecules in the electronic field on their spectra.[7]

The alkoxy-anhydrides fall into three types :

Type I : anhydrides II*a*, *b*, and *c*; and III*a* and *b*.

Type II : anhydrides I*b*, *c*, and *d*; II*d*; and III*c*.

Type III : anhydrides I*e*, *f*, and *g*; and IV.

The main excited structures of the three types are shown on p. 400 :

In type I, the main excitation is oriented vertically along ring *a*, and it is connected with the shifts 360→390 mμ in comparison with the parent anhydride. In type II, the main contributing coplanar structures are those resulting from excitation along the diagonal axis involving rings *a* and *b*; the effect of this excitation is reflected in the shifts 260→290 mμ. In type III both the diagonal and the vertical excitation (along ring *b*) lead to coplanar structures, which contribute to the actual state of the molecule, and the result is the combined effect.

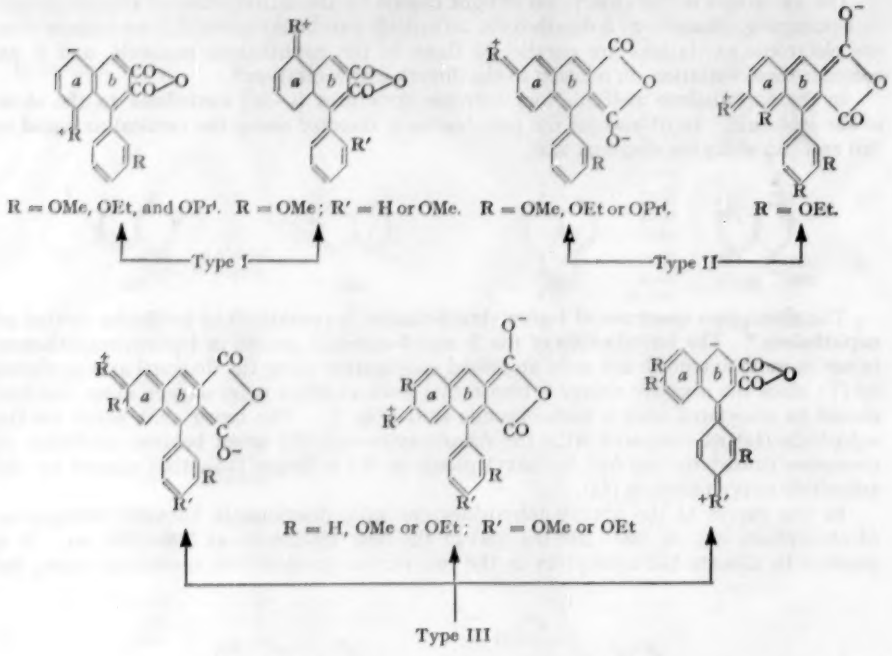
Comparison of the curves of these alkoxy-anhydrides with those of 1-phenylnaphthalene and 2-phenylnaphthalene[6,8] reveals the similarity of type I curves to that of 1-phenylnaphthalene on the one hand, and the close relation of type II curves to 2-phenylnaphthalene on the other, although all type I and type II curves are for 1-phenylnaphthalene derivatives. The difference in the curves of 1- and 2-phenylnaphthalene has been assigned

[5] Jones, *Chem. Rev.*, 1947, **41**, 353.

[6] *Idem*, *ibid.*, 1943, **32**, 1.

[7] Scheibe, *Kolloid Z.*, 1938, **82**, 1; *Angew. Chem.*, 1939, **52**, 631; Lewis and Bigeleisen, *J. Amer. Chem. Soc.*, 1943, **65**, 520, 2102, 2107; Lewis and Calvin, *Chem. Rev.*, 1939, **25**, 273; Zechmeister, LeRosen, Schroeder, Polgár, and Pauling, *J. Amer. Chem. Soc.*, 1943, **65**, 1940; Zechmeister, *Chem. Rev.*, 1944, **34**, 267; and Mulliken, *J. Chem. Phys.*, 1939, **7**, 364.

[8] Friedel, Orchin, and Reggel, *J. Amer. Chem. Soc.*, 1948, **70**, 199.



to a coplanarity effect.[6] Friedel, Orchin, and Reggel,[8] however, attributed the bathochromic shifts and the greatly decreased fine structure in the spectrum of 1-phenylnaphthalene (compared with that of naphthalene) to an appreciable contribution from coplanar resonance structures involving the phenyl and the naphthalene ring. This conclusion receives support from the curves for type III anhydrides in the present series. It, therefore, appears that coplanarity effects are not the factor that governs the general features of the spectrum of the phenylnaphthalenes. Most probably this factor lies in the directional effects.

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80. *A Spectrophotometric Study of Hexanitrodiphenylamine. Part I. The Molecular and Ionic Forms in Dioxan.*

By S. Kertes and J. M. E. Goldschmidt.

Hexanitrodiphenylamine, in its yellow and its red form, was investigated potentiometrically and spectrophotometrically in dioxan solution. It was found to be a strong acid, and its red form is an anion of an *aci*-nitro-acid. The potassium salt, which is insoluble in water, was studied in dioxan solution and found to be a simple salt.

2 : 2′ : 4 : 4′ : 6 : 6′-Hexanitrodiphenylamine, also known as dipicrylamine, is used as a precipitant for potassium.[1] Treadwell and Hepenstrick [2] determined its solubility and dissociation constant in water, and Schroeder *et al.*[3] investigated its absorption spectra in absolute ethyl alcohol but did not discuss the results.

The possibility of the existence of tautomeric forms of aromatic nitro-compounds was discussed by Hantzsch and Lister,[4] but the problem is still under discussion.[5] Feigl [6] discusses the different forms of aromatic nitro-compounds, and in particular hexanitrodiphenylamine, postulating the existence of *baso*- and *aci*-forms. In addition he suggests the possibility that the potassium salt is an inner complex salt on the basis of its slight solubility in water, its stability against mineral acids, and its solubility in organic nitro-compounds.

Our object was to study the *baso*- and *aci*-forms of the amine, their conditions of existence, and their relationship to each other and to the potassium salt. Part II will deal with these interrelationships in various organic solvents.

Experimental

Reagents.—The hexanitrodiphenylamine was an Eastman Kodak Reagent for laboratory use, and was not recrystallized. The potassium and sodium hydroxides used were " Baker's Analyzed " C.P. reagents. Dioxan (B.D.H.) was not further purified before use. Absolute ethyl alcohol was used.

0·01M-Solutions of hexanitrodiphenylamine were prepared by dissolving the yellow crystals in dioxan. Fresh solutions were always used since these solutions are unstable, becoming appreciably orange in 24 hr., and consequently unsuitable for measurements. Solutions of 0·1M- and 0·01M-potassium and sodium hydroxide were prepared by diluting a 1·0M-solution in absolute ethyl alcohol with dioxan.

Apparatus.—A Beckman Model G pH-Meter in conjunction with a glass–calomel electrode system, and a Beckman Model DU Spectrophotometer with a hydrogen lamp and matched 10 mm. quartz cells were used. Measurements in the visible range were made by using a tungsten lamp and 10-mm. Beckman glass cells.

Procedure.—The potentiometric titrations were carried out by titrating 30 ml. of 0·01M-amine with 0·1M-potassium hydroxide in increments of 0·01 ml. from a microburette of 5 ml. capacity, whose tip dipped into the solution. The solution was mechanically stirred. It took several seconds for the readings of the pH meter to become constant.

For the spectrophotometric measurements the reference solution had the same solvent composition as the measured solution.

Results.—Determination of dissociation constant. Fig. 1 shows the potentiometric titration curve of a dioxan solution of hexanitrodiphenylamine with potassium hydroxide : it is typical for the titration of a strong acid with a strong base. The apparent pK_a is 0·35 ($K_{(app.)}$ = 0·46), which is of the same order of magnitude as that of picric acid in water.

Effect of neutralization on absorption curves. The absorption curves in the presence of

[1] Kolthoff and Bendix, *Analyt. Chem.*, 1939, **11**, 94; Amdur, *ibid.*, 1942, **14**, 731; Cotton, *ibid.*, 1945, **17**, 734; Welcher, " Organic Analytical Reagents," Vol. IV, Van Nostrand Co., New York, 1948, p. 8.
[2] Treadwell and Hepenstrick, *Helv. Chim. Acta*, 1949, **32**, 1903.
[3] Schroeder, Wilcox, Trueblood, and Dekker, *Analyt. Chem.*, 1951, **23**, 1740.
[4] Hantzsch and Lister, *Ber.*, 1910, **43**, 1685.
[5] *E.g.*, see reviews by Ferguson, " Electronic Structures of Organic Molecules," Prentice Hall Inc., New York, 1952; Baker and Taylor, " Sidgwick's Organic Chemistry of Nitrogen," Oxford Univ. Press, 1942.
[6] Feigl, " Chemistry of Specific, Selective, and Sensitive Reactions," Academic Press Inc., 1949, p. 282.

potassium hydroxide are shown in Fig. 2: the alkali causes a shift from the yellow to the red which effectively reaches its maximum when the stoicheiometrical quantity of potassium hydroxide needed to neutralize the hexanitrodiphenylamine present has been added. In dioxan solution this shift is from 430 to 560 mμ at an extinction value of 1·0. A similar effect of the same order of magnitude was observed when using sodium hydroxide instead of potassium hydroxide.

Effect of added water on the absorption curves. The effect of added water on the partial

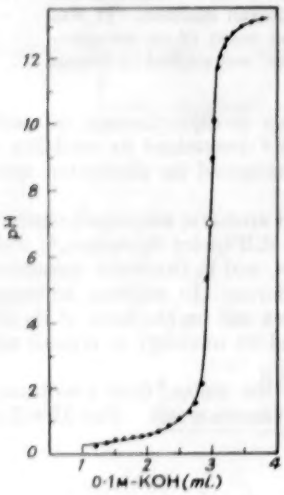


FIG. 1. *Potentiometric titration curve of* 30 *ml. of* 0·01M-*hexanitrodiphenylamine with* 0·1M-*potassium hydroxide in dioxan.*

FIG. 2. *Effect of added potassium hydroxide on the absorption curves of hexanitrodiphenylamine.*

Composition: 0·01M-Hexanitrodiphenylamine (2 ml.), 0·01M-potassium hydroxide (*x* ml.), dioxan [(18 − *x*) ml.].

Percentage neutralisation: 1, 0; 2, 20; 3, 40; 4, 60; 5, 80; 6, 100; 7, 200; 8, 300%.

FIG. 3. *Effect of added water on the absorption curves of hexanitrodiphenylamine.*

Composition: 0·01M-Hexanitrodiphenylamine (2 ml.), water (*x* ml.) dioxan [(18 − *x*) ml.].

Concentration of water (%): 1, 0; 2, 10; 3, 20; 4, 30; 5, 40; 6, 50; 7, 60; 8, 70%.

FIG. 3.

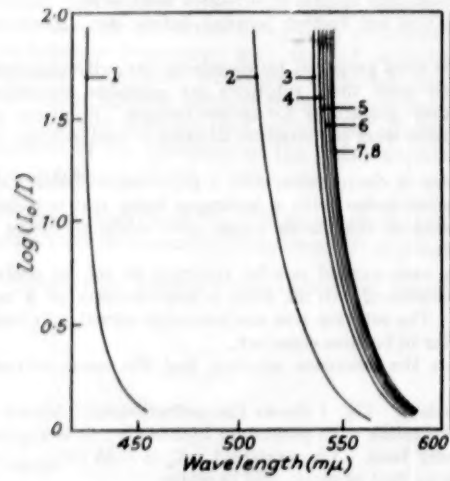
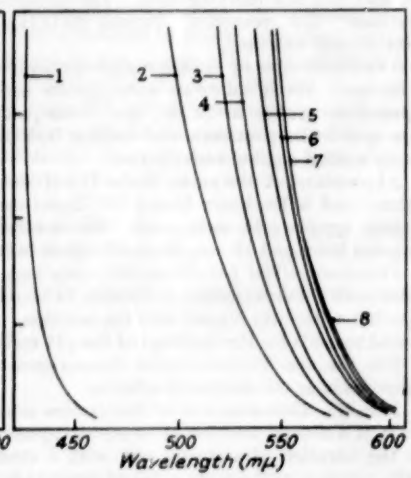


FIG. 2.



spectrum of a dioxan solution is shown in Fig. 3: the water causes a shift of the absorption curve towards longer wavelengths, the maximum effect (from 430 to 550 mμ) being substantially achieved with 20% of water. With more than 70% of water, hexanitrodiphenylamine is precipitated.

Ultraviolet absorption spectra. Fig. 4 shows the absorption spectra from 250 mμ to 520 mμ of the amine under different conditions. As can be seen, the minimum which occurs in curve (1) at 345 mμ has moved to roughly 300 mμ in curves (2) and (3), and the maximum at 355 mμ has shifted to 415 mμ. Although the amount of amine is the same in all three experiments, it is

obvious that the absorbance is very roughly twice as large in (2) and (3) as in (1). No measurements could be made at wavelengths below 250 mμ, since dioxan itself absorbs strongly.

Effect of acids and electrolytes on colours. Qualitative tests were made to detect the influence of various acids and electrolytes on the yellow and the red form of hexanitrodiphenylamine in dioxan. Addition of concentrated sulphuric, nitric, hydrochloric, or acetic acid to the yellow form caused no change. Addition of lithium, sodium, or potassium nitrate solution to a yellow amine solution caused immediate formation of a deep red colour (the salt solutions were in 1 : 3 ethanol–dioxan—a blank test gave no colour change). On the addition of water to an acidified yellow solution the red form did not appear before the precipitation of the yellow solid took place. The red solution in dioxan, which had been prepared by adding a little sodium nitrate to the yellow solution, became yellow on the addition of concentrated hydrochloric acid. Glacial acetic acid had no effect on the colour.

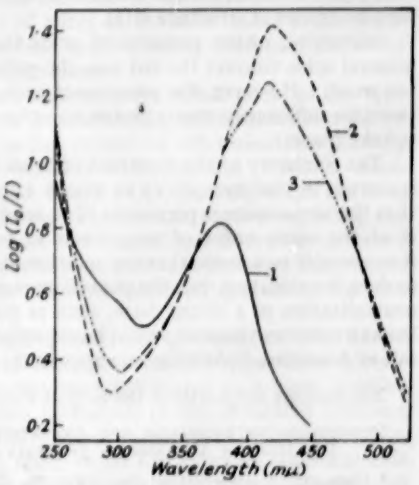
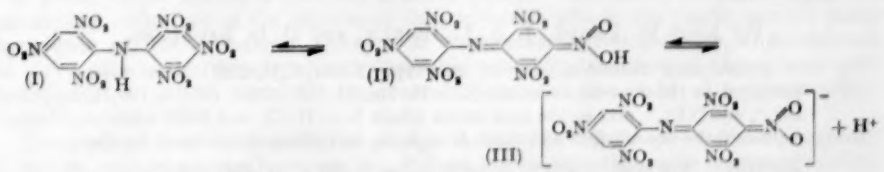


FIG. 4. *Absorption spectra of hexanitrodiphenylamine* (5×10^{-5}M).

1, In dioxan; 2, in 3 : 7 v/v water-dioxan; 3, in dioxan in presence of $1{\cdot}5 \times 10^{-4}$M-potassium hydroxide.

DISCUSSION

On the basis of the work of Hantzsch and Lister [4] and in accordance with the suggestion of Feigl,[6] it can be assumed that hexanitrodiphenylamine exists in two forms (I; yellow) and (II; red). As seen from the determination of the dissociation constant, form (II) is a



strong acid, dissociating into the ionized form (III) which will be the stable form. Therefore, it appears that (I) is the yellow crystalline form that is synthesized, being insoluble in water but readily soluble in non-polar solvents, whilst (III) is the red form, being an *anion* whose sodium salt is very soluble in water and in organic solvents. The intense colour is doubtless derived from the continuous system of conjugated double bonds, and from the possibility of ionic resonance existing in the anion, since both *para*-nitro-groups and all four *ortho*-nitro-groups are equivalent as far as each can become the *aci*-nitro-group. This effect would cause the stabilization and deepening of the colour.

According to Brönsted's definition of acids and bases, structure (I) can only be stable in the absence of proton-acceptors, which is the case with dioxan, it being too weak a

proton-acceptor to effect the ionization of hexanitrodiphenylamine. The conversion into the red form requires a proton-acceptor. The experiments in which water was added to the yellow dioxan solution, changing it gradually to red, show that even water (a weak proton-acceptor) is sufficiently strong to cause the dissociation of structure (I) to (III). This dissociation is complete, if it is assumed that hydroxyl ions effect complete ionization, since the shift caused by the addition of 20% of water is substantially equal to the shift caused by the addition of hydroxyl ions, which are very strong proton-acceptors. The fact that so weak a proton-acceptor as water can cause complete dissociation is additional proof of the strength of the amine as an acid. Concerning its stability in water, Ungnade [7] found that polar solvents, such as water, would tend to stabilize polar quinonoid resonance forms such as anions of structure (III).

Naturally, in the presence of acids the concentration of the anion is repressed. All mineral acids convert the red into the yellow form, but acetic acid in dioxan is apparently too weak. However, the presence of neutral electrolytes, such as the alkali-metal nitrates, provides sufficiently strong proton-acceptors for the conversion into the anion structure (III) to take place.

The similarity of the spectrum of hexanitrodiphenylamine in 30% water in dioxan to its spectrum in the presence of an excess of potassium hydroxide in dioxan seems to suggest that the same anion is present in both solutions. Likewise the shift in the partial spectrum is of the same order of magnitude in both cases (Figs. 2 and 3). These facts make it reasonable to assume that the solution of the potassium salt contains the same free anions as does the acid, and that the potassium is not bound to the anion in an inner complex. The neutralization of a strong base, such as potassium hydroxide, with a strong acid, such as hexanitrodiphenylamine, would be expected to give a fully ionized salt, which the potassium salt of hexanitrodiphenylamine appears to be.

The authors acknowledge the help of Professor M. Bobtelsky of this Department.

Department of Inorganic and Analytical Chemistry,
The Hebrew University, Jerusalem, Israel. [*Received, August 15th*, 1955.]

[7] Ungnade, *J. Amer. Chem. Soc.*, 1953, **75**, 432.

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81. *Mechanism of Aromatic Side-chain Reactions with Special Reference to the Polar Effects of Substituents. Part XVI.* Hyperconjugation of Groups of the Type* CH_2X *in the Benzaldehyde–Cyanohydrin Equilibria.*

By John W. Baker, J. A. L. Brieux, and D. G. Saunders.

Substituted benzaldehydes of the type $X{\cdot}CH_2{\cdot}C_6H_4{\cdot}CHO$ have been prepared in the *para*-series where X = H, Me, Cl, OH, OMe, CO_2Et, CO_2H, CO_2^-, and NEt_3^+, and in the *meta*-series where X = H, Cl, and OMe, and the values of the equilibrium constants $K = k_2/k_1$, have been determined for the reaction $X{\cdot}CH_2{\cdot}C_6H_4{\cdot}CHO + HCN \underset{k_2}{\overset{k_1}{\rightleftharpoons}} X{\cdot}CH_2{\cdot}C_6H_4{\cdot}CH(OH){\cdot}CN$ in constant-boiling alcohol at 20°. The results provide information regarding the effect of the substituent X on the hyperconjugation of the group CH_2X and are discussed on this basis.

It has been clearly demonstrated [1] that the equilibrium $R{\cdot}C_6H_4{\cdot}CHO + HCN \underset{k_2}{\overset{k_1}{\rightleftharpoons}} R{\cdot}C_6H_4{\cdot}CH(OH){\cdot}CN$ constitutes a very favourable system for determination of the relative mesomeric electron-release (+*M*) effects of the substituents R, even when such substituents

* Part XV, *J.*, 1952, 2831.

[1] (*a*) Baker and Hemming, *J.*, 1942, 191; (*b*) Baker and Hopkins, *J.*, 1949, 1089; (*c*) Baker, Barrett, and Tweed, Part XV, *J.*, 1952, 2831.

possess dual polar effects of the types $\pm I$, $+M$. This communication records the use of this equilibrium in an attempt to ascertain the effect of various groups X on the H–C hyperconjugation [2] of CH_2 in the group CH_2X. The method depends essentially on the fact that, because of the more extended conjugated system present, mesomeric electron-release by a *para*-substituent R effects relatively greater stabilisation of the free aldehyde *p*-R·C_6H_4·CHO than of its cyanohydrin *p*-R·C_6H_4·CH(OH)·CN. Hence the increase in the numerical value of the equilibrium constant, $K = k_2/k_1$, is a measure of the relative mesomeric effect of the group R. In the *meta*-position the inductive effect of the substituent will be the dominating influence (with only minor complications arising from a relayed, second-order mesomeric effect [1b]), so that the ratio of the equilibrium constants K_p/K_m gives a more reliable assessment of the $+M$ effect of the substituent in the *para*-position. Wherever this supplementary test has been applied it has confirmed the order of $+M$ effects deduced from a study of the *para*-series alone.

It was intended to determine such equilibrium constants for substituents of the type CH_2X in both the *meta*- and the *para*-position in benzaldehyde but certain unexpected experimental difficulties in the *meta*-series have, so far, permitted determinations for only three such *meta*-substituted benzaldehydes, *viz.*, when X = H, Cl, and OMe. A much more extended range, X = H, Me, OH, OMe, CO_2Et, CO_2H, CO_2^-, Cl, and NEt_3^+, has been studied in the *para*-series. Since it seems unlikely that further information regarding the *meta*-series will become available in the near future, it is considered desirable to record the results already obtained, especially as they seem to justify certain tentative conclusions regarding the effect of various groups X on the effective hyperconjugation of the two H–C bonds in the whole group CH_2X.

Methods for the preparation of the required aldehydes (most of which are new) varied from case to case and are given in the Experimental section. Certain irregularities in yield obtained by Stephen's method [3] from *p*-chloromethylbenzonitrile led to a more detailed examination in this case. Under usual conditions hydrolysis of the separated aldimine stannichloride with water at 70° gave only a 17% yield of *p*-chloromethylbenzaldehyde. Concentration of the supernatant ether solution, from which the aldimine stannichloride had separated, and hydrolysis of the solid so obtained with water at 30° afforded unchanged *p*-chloromethylbenzonitrile (17%) and *p*-chloromethylbenzamide, characterised by alkaline hydrolysis to ammonia and *p*-hydroxymethylbenzoic acid, conversion into *p*-chloromethylbenzoic acid with nitrous acid, and dehydration to the original nitrile with phosphoric oxide. Continuous ether-extraction of the combined aqueous extracts afforded, in addition to various tin-containing products, *p*-hydroxymethylbenzaldehyde, which is very soluble in water and was characterised as its 2 : 4-dinitrophenylhydrazone. Thus the main causes of the low yield of *p*-chloromethylbenzaldehyde are (1) incomplete reaction of the nitrile or its hydrogen chloride addition product with stannous chloride so that subsequent hydrolysis of the unreduced chloroaldimine affords the amide, and (2) ready hydrolysis of the side-chain chlorine in *p*-chloromethylbenzaldimine stannichloride to give water-soluble *p*-hydroxymethylbenzaldehyde. Modifications in the experimental technique (see p. 410) based on these results increased the yield of *p*-chloromethylbenzaldehyde to 72·5%.

Determination of the equilibrium constants was effected by the method previously described, with tri-*n*-propylamine as the catalyst, but modifications were necessary in some cases because of secondary reaction of the benzyl side-chain with the reagents used in the determination of hydrogen cyanide. Thus with CH_2Cl·C_6H_4·CHO a small, experimentally-determined correction was necessary for the reaction of the side-chain chlorine with silver nitrate under strictly standardised conditions of titration. Because of the much greater reactivity of bromine and iodine, equilibrium determinations with the bromomethyl- and iodomethyl-derivatives were not possible. With *p*-{$^+NEt_3$·CH_2·C_6H_4·CHO}Cl^- there is a large correction for the reaction of the chloride ion with silver nitrate. In the study of the aldehydo-acid, *p*-HO_2C·CH_2·C_6H_4·CHO, the basic catalyst would be removed by conversion into the salt and hence the very slow equilibration of the cyanohydrin reaction had to be

[2] Cf. Baker, "Hyperconjugation," Clarendon Press, Oxford, 1952, p. 96.
[3] Stephen, *J.*, 1925, **127**, 1874.

followed over a long period. For such reasons the values of the equilibrium constants may not be quite as accurate as those previously determined in more straightforward cases, but the consistency of the values obtained in a number of determinations (Table) indicates that they are sufficiently reliable as data from which conclusions may be drawn regarding the relative mesomeric electron-release of the various groups.

The results are given and analysed in the Table. The values of ΔF are calculated from the usual relation $\Delta F = -RT \ln K$.

Equilibrium constants $K = k_2/k_1$ *for the reaction* $X{\cdot}CH_2{\cdot}C_6H_4{\cdot}CHO + HCN \underset{k_2}{\overset{k_1}{\rightleftharpoons}} X{\cdot}CH_2{\cdot}C_6H_4{\cdot}CH(OH){\cdot}CN$ *in constant-boiling alcohol at* 20°. *Catalyst* = 2 *drops* (~0·003M) *of* NPr^n_3 *in* 50 *ml. of a solution initially* 0·1M *with respect to aldehyde and* ~0·16M *with respect to* HCN.

X [a]	10^3K (mole l.$^{-1}$)	No. of determns.	$10^{-3}\Delta F$ (cal.)	$10^{-3}\delta(\Delta F) = \Delta F_H - \Delta F_{CH_2X}$ (cal.)	$10^{-3}\delta$ (ΔF) per H (cal.)
H *p* [b]	8·74 ± 0·08	4	27·6	−3·9	−1·3
m	5·5 ± 0·1	6	30 3	−1·2	−0·4
CO_2^-	8·96 ± 0·1	3	27·4	−4·1	−2·0$_5$
Me [b]	8·18 ± 0·03	—	28·0	−3·5	−1·7$_5$
OH	7·57 ± 0·16	7	28·4	−3·1	−1·5
MeO *p*	3·81 ± 0·07	5	32·4	+0·9	+0·45
m	3·7 ± 0·1	5	32·6	+1·1	+0·5$_5$
CO_2Et	5·22 ± 0·21	6	30·6	−0·9	−0·4$_5$
CO_2H	6·64 ± 0·21	2	29·2	−2·3	−1·1$_5$
Cl *p*	8·34 ± 0·21	8 [c]	27·9	−3·6	−1·8
m	4·9 ± 0·4	2	30·9	−0·6	−0·3
NEt_3^+	12·52 ± 0·11	7 [d]	25·5	−6·0	−3·0
($CH_2X = H$) [b]	4·47 ± 0·11	—	31·5	—	—

[a] In *p*-position except where otherwise shown. [b] Baker and Hemming [10a] whose value for *p*-Me·C_6H_4·CHO was 8·98. [c] NPr^n_3 = 0·0015M. [d] Catalyst = 0·003M-NEt_3.

Discussion.—Most of the somewhat sparse evidence for the hyperconjugation effects of groups of the type CH_2X is derived from reaction rates and thus applies to the total $+T$ effect, *i.e.*, mesomeric plus electromeric. Partial-rate factors for the nitration of ethyl phenylacetate [4] show that, in this compound, the group $\cdot CH_2{\cdot}CO_2Et$ has a negligible inductive effect whilst appreciable activation of the *ortho*- and *para*-positions reveals a considerable $+E$ effect due to hyperconjugation of the two H–C bonds. Similar results for benzyl chloride [4] indicate a strong $-I$ effect superimposed on a $+E$ (hyperconjugative) effect for the group $\cdot CH_2Cl$. For groups $\cdot CH_2R$ (R = alkyl), Berliner and Berliner [5] have explained the different polar effects on the rates of bromination of aromatic compounds by assumption of a second-order type of hyperconjugation but Baddeley, Chadwick, and Rawlinson [6] pointed out that an alternative explanation, based on the geometric requirements of first-order hyperconjugation of the H–C_α bonds, is possible.[7] Theoretical calculations,[8] based on electrostatic field effects in the transition state, of the percentage of *meta*-isomeride produced in electrophilic substitution in benzene derivatives are in agreement with experimental values for those groups which have neither unshared electron pairs nor hyperconjugating H–C bonds, but for the groups Me, $CH_2{\cdot}CN$, $CH_2{\cdot}NH_3^+$ $CH_2{\cdot}NO_2$, and $CH_2{\cdot}CH_2{\cdot}NO_2$ the theoretical values are all much higher than the experimental, indicating considerable *ortho-para*-activation arising from hyperconjugation of the CH_2X group with the benzene ring in the transition state of substitution. Relative rates (C_6H_6 = 1) for the unimpeded *para*-bromination of compounds PhR with molecular bromine were determined by Robertson, de la Mare, and Swedlund [9] who, for groups of the $-I$, $+T$ type, found R = CH_2Ph, 51; $CH_2{\cdot}CO_2Et$, 2·3; CH_2Cl, 0·76; $CH_2{\cdot}CN$, 0·17. Increasing inductive electron-attraction in the series Ph < CO_2Et < Cl < CN partly

[4] Ingold and Shaw, *J.*, 1949, 575.
[5] Berliner and Berliner, *J. Amer. Chem. Soc.*, 1949, **71**, 1195 and later papers.
[6] Baddeley, Chadwick, and Rawlinson, *Nature*, 1949, **164**, 833; cf. Baddeley and Gordon, *J.*, 1952, 2190.
[7] Cf. Baker, ref. 2, p. 53.
[8] Sixma, *J. Chem. Phys.*, 1951, **19**, 1209.
[9] Robertson, de la Mare, and Swedlund, *J.*, 1953, 782.

accounts for the reduction of velocity in this series, but the overall activation by $CH_2{\cdot}CO_2Et$ evidently arises from hyperconjugation, whilst the deactivating $-I$ effect of CH_2Cl and $CH_2{\cdot}CN$ is probably partly compensated by an activating $+E$ effect of these groups. Similar results [10] for the rate of addition of bromine to allyl derivatives of the type $\overset{\alpha}{CH_2X}\!-\!\overset{\beta}{CH}\!=\!\overset{\gamma}{CH_2}$ were :

X	F	Cl	Br	CN
k_2^{25}	2·9	1·6	1·0	0·23

It was shown that attack is initiated by electrophilic bromine at C_γ and is thus facilitated by electron-release by CH_2X. Hence the group CH_2F exhibits a greater electron-releasing capacity than CH_2Br and CH_2Cl in spite of the increasing $-I$ effect $Br < Cl < F$. Such results suggest that hyperconjugative electron-release by the group CH_2X *may* be increased by increasing electron-*attraction* of X.

On the other hand Burton and Ingold [11] determined the proportions of αβ- and αδ-dihydro-compounds formed by reduction of substituted vinylacrylic acids with metal amalgams in alkaline and acid media. In interpretation of these results, de la Mare, Hughes, and Ingold [12] postulated that, since the direction of electron distribution in hyperconjugation is unambiguously $Alk\!-\!C\!=\!C$, the importance of such hyperconjugation in groups CH_2X would decrease in the series $X = CO_2^- > H > CO_2H$. This implies that hyperconjugation is greater the larger is the electron-*release* effect of X.

It is recognised that, just as the polarisability component ($+E$) of hyperconjugation may vary according to the electron-demand of the reaction (cf. for example, the difference between nitration with NO_2^+ and bromination with molecular bromine [9]), so the permanent polarisation ($+M$) may be greater the more extended is the conjugated system to which the group is attached.[13] Hence the extended conjugated system in benzaldehyde may evoke a greater degree of hyperconjugation than is present in the vinylacetic acids. The results in the Table suggest that, in our system at least, electron-release by the group X is *not* the factor which increases the degree of hyperconjugation of the whole group CH_2X, since the strongly electron-attracting ammonium pole in $CH_2{\cdot}NEt_3^+$ seems to confer even greater hyperconjugation on the whole group than does the strongly electron-repelling anion in the group $CH_2{\cdot}CO_2^-$. Reasons have already been adduced [13] why a $-I$ effect should destabilise the free aldehyde relative to its cyanohydrin (and hence lower the value of K), and were experimentally confirmed for the unequivocally $-I$ groups, halogen and nitro, in the *meta*-position. The much higher K value observed in the cation p-$^+NEt_3{\cdot}CH_2{\cdot}C_6H_4{\cdot}CHO$ would thus appear to arise from a considerable $+M$ (hyperconjugative) effect of the group $CH_2{\cdot}NEt_3^+$.

There is now considerable support for the original view [13] that the degree of hyperconjugation decreases as the number of hyperconjugated H–C bonds is reduced. Hence, to get a consistent standard for the effect of the substituent X on the relative degree of hyperconjugation of group CH_2X, in comparison with that of CH_3, the changes in free energy of dissociation of the cyanohydrin for a single hyperconjugated H–C bond are given in the last column of the Table. It is recognised that this value will include contributions to the relative stability of the free aldehyde from the inductive effect of CH_2X. In the Table the groups are arranged in the order * of decreasing $+I$ (or increasing $-I$) effects of X and hence, presumably, of CH_2X also. Sole operation of this inductive effect should thus, for the *para*-substituents, cause a gradual decrease in the (negative) value of $\delta(\Delta F)$ in passing down the Table. Irregularities observed must be due to some other polar factor, most probably hyperconjugation.

* The less obvious differences in this order are justified by various observations in the literature.[14]

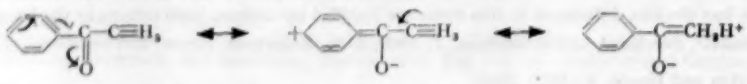
[10] Swindale, Swedlund, and Robertson, *J.*, 1950, 812; Robertson, Heyes, and Swedlund, *J.*, 1952, 1014.
[11] Burton and Ingold, *J.*, 1929, 2022.
[12] de la Mare, Hughes, and Ingold, *J.*, 1948, 25.
[13] Baker and Nathan, *J.*, 1935, 1844; Baker, *J.*, 1939, 1150.
[14] References quoted by Saunders, Thesis, Leeds, 1955.

Before discussing the superficially random effects of X revealed by these K values it should be noted that the closely similar values of K for *p*-Me (8·74) and *p*-CH_2Cl (8·34) are confirmed by the close similarity of their ratios K_p/K_m which are, respectively, 1·6 and 1·7. Although slender, this evidence supports our contention that the values of K for other *para*-substituents do give at least a correct qualitative order of their $+M$ effects, even where results for the *meta*-derivative are not available. The differences in the $\delta(\Delta F)$ values for *meta*- and *para*-substitution indicate that the mean relative stabilisations of the aldehyde to the cyanohydrin for each hyperconjugated H–C bond in the groups Me and CH_2Cl are, respectively, 90 and 150 cal./mole, values of the expected order of magnitude.

In any discussion of these results it is recognised that, although the K values are well spaced, the extreme difference in ΔF is only ~700 cal., a small value in relation to various unknown energy and entropy factors such as the change in solvation due to the introduction of integrally charged centres into the molecule. Hence any explanations can be only very tentative. Such uncertainties are, however, unavoidable in any experimental approach to the problem, because of the small energy contributions associated with hyperconjugation even in favourable systems. Two explanations are possible. The first is based on the hypothesis that hyperconjugation of the group CH_2X is *increased* by electron-*attraction* of the group X. This view is supported by the observation that, although the partial-rate factors for the *meta*-position in the nitration of ethyl phenylacetate and benzyl chloride [4] prove an order of $-I$ effects $CH_2Cl > CH_2{\cdot}CO_2Et$, nevertheless the equilibrium K value for *p*-chloromethylbenzaldehyde is much larger than that for ethyl *p*-formylphenylacetate, thus revealing a greater hyperconjugation effect by the former group. In the series $X = CO_2^-$, Me, OH, CO_2Et, CO_2H, Cl, NEt_3^+, the inductive electron-release ($+I$) effect decreases (or $-I$ increases). This factor should cause a gradual and continuous fall in the value of K. At the same time the hyperconjugative electron-release of CH_2X will, *ex hypothesi*, increase, and cause a gradual and continuous rise in the value of K. Superimposition of these two opposing polar effects would thus cause the value of K to pass through a minimum in the above series, in accord with experimental findings. On this view the reduction of hyperconjugative electron-release of groups of the type $CH_2{\cdot}COR$ is regarded as due to crossed hyperconjugation of the CH_2 group with the group COR and with the benzaldehyde residue (see *A*). The greater the $+M$ effect of R in satisfying the

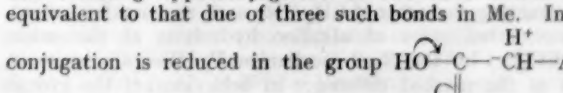
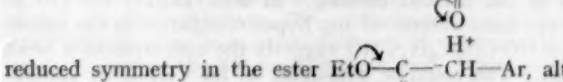
electron-demand of the CO group in COR, the smaller should be the competition of the crossed hyperconjugation of the CH_2 group, and hence the hyperconjugation of the whole group $CH_2{\cdot}COR$ with the benzene ring should (as is found) decrease in the order $R = O^- > OH > OEt$. The *total* electron release of the group $CH_2{\cdot}COR$ ($+I$, $+M$) will, however, be complicated by a strong $+I$ effect when $R = O^-$.

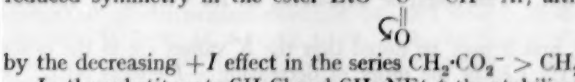
An alternative explanation of our results is possible by a modification of this view if it is tentatively assumed that the main effect of the group X is due not so much to its electron-attracting power as to its ability to stabilise further the negative charge in structures of the general type (*B*) which are involved in hyperconjugation. Rothstein has used a somewhat similar concept to formulate the structures of disulphonylpropenes, and the operation of a $-E$ effect of the sulphone in the transition state of the nitration of alkyl benzyl sulphones (due, in these examples, to the utilisation of the *d*-orbitals of sulphur). A further illustration is provided by the stimulation of the hyperconjugative effects of alkyl groups by the phenyl group in alkyl phenyl ketones,[16] *e.g.*:



[15] Rothstein, *J.*, 1937, 309; 1953, 3991.
[16] Baker, *Trans. Faraday Soc.*, 1941, **37**, 648.

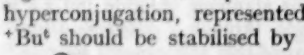
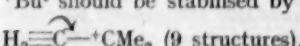
which explains why the cyanohydrin equilibrium constants of the alkyl phenyl ketones Ph·COAlk follow the order of the hyperconjugative effects of the alkyl group (K = Me > Et > Pr^i > Bu^t) whereas in the corresponding alkyl *cyclo*hexyl ketones [17] they are governed by the inductive effect (K = Me < Et < Pr^i).

In our present examples, application of this concept is most obvious in the group $CH_2{\cdot}CO_2^-$ where the structure $^-O{\cdot}CO{\cdot}C^-H{\cdot}C_6H_4{\cdot}CHO$, in which two negative charges may be distributed between two oxygen atoms and the formylbenzyl structure, may be regarded as simulating the resonance stabilisation in the symmetrical carbonate anion . The resulting hyperconjugation of two H–C bonds is thus rendered approximately equivalent to that due of three such bonds in Me. In harmony with this view hyperconjugation is reduced in the group  , and still more by the further reduced symmetry in the ester  , although differences are magnified by the decreasing $+I$ effect in the series $CH_2{\cdot}CO_2^- > CH_2{\cdot}CO_2H > CH_2{\cdot}CO_2Et$.

In the substituents CH_2Cl and $CH_2{\cdot}NEt_3^+$ the stabilisation of the negative charge must be assumed to arise from the strong electron-attracting effect of NEt_3^+ and, to a smaller extent, of Cl, an effect which is probably purely electrostatic, *viz.*,  . The prototropic mobility of propene systems activated solely by NR_2^+ groups is small but detectable,[18] and hence the group $CH_2{\cdot}NEt_3^+$ may possess weakly acidic character and some interaction between the basic catalyst and the positive hydrogens of the CH_2 group cannot be completely excluded, although it is regarded as negligible because of the high stoicheiometric ratio (~350 : 1) of aldehyde : tri-*n*-propylamine.

The marked hyperconjugative power of the group $CH_2{\cdot}NR_3^+$ might also be expected in an extended grouping of the type $^+NHR_2{\cdot}C_6H_4{\cdot}CH_2{\cdot}$ and so provide a satisfactory explanation of the ready bromination [19] of the di-cation of di-*p*-alkylaminophenylmethane in the 2 : 2′-positions by Br^+. *meta*-Orientation of electrophilic substitution in an attached benzene ring by groups NR_3^+ is known to arise from marked *deactivation* of the benzene ring positions in the order *o*, *p* ⩾ *m*, the electrophilic substituent entering the least deactivated position at a rate much slower than that in unsubstituted benzene. The ready bromination of di-*p*-alkylaminophenylmethanes with bromine–silver sulphate in concentrated sulphuric acid thus seems to result from re-activation of the 2 : 2′(*ortho*)-positions by the hyperconjugative ($+E$) effect of the CH_2 group (see *C*). That these positions are also the least deactivated by the $-I$ effect of the *m*-NR_2H^+ group we regard as incidental, rather than as the main reason for the observed orientation of bromination.

(*C*)

The suggestion that the main feature involved in the effect of the substituent X in increasing the hyperconjugation of the whole group CH_2X lies in its capacity for further stabilisation of the charge in one structure of the hyperconjugated hybrid is capable of logical extension to explain the postulated hyperconjugation of a Bu^t–C bond.[20] In such hyperconjugation, represented as Bu^t–C–C–X ⟷ $^+$Bu^{t}C=CX$^-$, the *positive* charge on $^+$Bu^t should be stabilised by ordinary H–C hyperconjugation from the methyl groups  (9 structures), thus visualising an overall hyperconjugation of the type  .

[17] D. P. Evans and Young, *J.*, 1954, 1310.
[18] Ingold and Rothstein, *J.*, 1931, 1666.
[19] Gorvin, *J.*, 1955, 83.
[20] Hughes, Ingold, and Shiner, jun., *J.*, 1953, 3830, and references there cited.

As already stated, these ideas in no sense neglect the importance of purely inductive effects of the groups CH_2X. Earlier results for *p*-alkylbenzaldehydes [18] clearly reveal the superimposed operation of such effects since the apparent negative values of $\delta(\Delta F)$ per single hyperconjugated H–C bond (see Table) increase in the series Me (−1·3), Et (−1·7), Pr^i (−3·4), whilst the group value (−2·6) for the *p*-Bu^t compound must be mainly, if not exclusively, due to its relative stabilising $+I$ effect on the free aldehyde. For substituents CH_2X studied which possess a $-I$, destabilising effect on the free aldehyde, their hyperconjugative effects may, therefore, be underestimated.

The observed effects of CH_2·OH and CH_2·OMe are difficult to interpret since their *K* values are well spaced on opposite sides of the value for unsubstituted benzaldehyde. The closely similar values of *K* for *m*- and *p*-MeO·CH_2·C_6H_4·CHO imply that only an inductive effect is operative in both positions and, moreover, that it is a weak overall electron-attracting effect. The electron-attracting character of CH_2·OMe and, to a smaller extent, CH_2·OH, is revealed in the accelerated rates of alkaline hydrolysis of the esters RO·CH_2·CO_2Et (relative to CH_3·CO_2Et) by the $B_{AC}2$ mechanism.[21] We can, however, offer no satisfactory explanation of the marked difference in behaviour of the groups CH_2·OMe and CH_2·OH or for the apparent absence of any hyperconjugation in the former group. The higher *K* value for *p*-HO·CH_2·C_6H_4·CHO suggests the operation of a weak hyperconjugative effect by CH_2·OH. This could be explained, as for CH_2Cl, by stabilisation of the type $HO\leftarrow{}^{-}\overset{H^+}{C}H\text{–}Ar$, and it may be noted that the *K* values are in the order *p*-$^+NEt_2$·CH_2 > Cl·CH_2 > HO·CH_2, *i.e.*, in the order of decreasing $-I$ effects NEt_3^+ > Cl > OH. In the case of CH_2·OH there are other possible complicating factors. One is the partial conversion into the anion $^-$O·CH_2·C_6H_4·CHO, although the concentration (and total amount) of basic catalyst present is very small. Another is the possibility of self-condensation of a hemiacetal type between the aldehyde group of one molecule and the primary alcohol group of a second. No such self-condensation could be detected under equilibration conditions but viscous condensation by-products were often encountered in the preparation of some of these formylbenzyl compounds, particularly with the *p*-hydroxymethyl derivative.

We have not discussed our results on the basis of the conception of Baddeley *et al.*[6] regarding the geometrical requirements for hyperconjugation of a CH_2X group because the largest group CH_2·NEt_3^+, which is the only one in which planarity with the benzene ring might be difficult, apparently exhibits the largest hyperconjugation. It therefore appears that this steric factor is not important in the examples we have studied.

Experimental

Microanalyses are partly by Mrs. Y. Richards, The University, Leeds.

Materials.—*m*-, b. p. 72·4°/10 mm., and *p*-Tolualdehyde, b. p. 85—86°/15 mm., were purchased samples, purified through their bisulphite derivatives and semicarbazones as previously described.

p-*Chloromethylbenzaldehyde.*—*p*-Toluidine was converted [22] into *p*-tolunitrile, m. p. 28°, which was chlorinated in the side chain (with illumination by a 500 w Nernst lamp) at its b. p. until 95% of the theoretical amount of chlorine had been absorbed, to give p-*cyanobenzyl chloride*, m. p. 81° after crystallisation from ligroin (b. p. 60—80°) (Found: Cl, 23·8. C_8H_6NCl requires Cl, 23·4%). After examination of the by-product formed when Stephen's reaction [3] was applied to this compound, the following technique for its conversion into the aldehyde was used. The important modifications are italicised. Anhydrous stannous chloride (80 g.) in 1400 ml. of dry ether was saturated with dry hydrogen chloride, through a *wide-bore delivery tube, at 0° until the oily complex which initially separated had passed into homogeneous solution.*[23] A solution of the nitrile (50 g.) in dry ether (400 ml.) was then added and the mixture was *completely* re-saturated with hydrogen chloride at 0°. Mechanical stirring was maintained

[21] Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons, London, 1954, p. 758, Table 47-2.

[22] *Org. Synth.*, Coll. Vol. I, 2nd Edn., p. 514.

[23] Cf. King, L'Ecuyer, and Openshaw, *J.*, 1936, 353; Evans and Walker, *J.*, 1947, 1572.

throughout. The mixture was then allowed to rise to room temperature and was *kept for* **3** *days*, with occasional stirring, to ensure complete separation of the aldimine stannichloride. The supernatant ether was then decanted and the washed precipitate was hydrolysed with water at 60—70° and, after the remaining ether had evaporated, the aqueous liquors were *immediately cooled* to minimise hydrolysis of the side-chain chlorine. The separated *p*-chloromethylbenzaldehyde solidified and was *filtered* off, and dissolved in ether. The supernatant aqueous solution was extracted with ether, the ethereal solution was washed with aqueous sodium carbonate and the combined ether solutions were dried (Na_2SO_4) and concentrated. This technique prevents the formation of emulsions which are obtained if the whole product is extracted with ether. When cooled, p-*chloromethylbenzaldehyde* crystallised and had m. p. 73°, after recrystallisation from ligroin (b. p. 40—60°) (Found : C, 61·9; H, 4·5; Cl, 23·1. C_8H_7OCl requires C, 62·15; H, 4·6; Cl, 22·9%) (yield, 38 g., 72·5%). Although this aldehyde combines with sodium hydrogen sulphite no crystalline derivative separates and regeneration affords a water-soluble aldehyde, probably *p*-hydroxymethylbenzaldehyde. Analysis of its semicarbazone, m. p. 205° (decomp.) after crystallisation from aqueous alcohol, indicates some reaction with side-chain chlorine (Found : C, 50·7; H, 5·1; Cl, 15·5. Calc. for $C_9H_{10}ON_3Cl$: C, 51·1; H, 4·8; Cl, 16·75%). Regeneration from the semicarbazone caused some hydrolysis of the side-chain chlorine. The aldehyde forms a 2 : 4-dinitrophenylhydrazone, m. p. 246° after crystallisation from acetic acid. With acetic anhydride and one drop of concentrated sulphuric acid at 40—50° for 0·75 hr. it gave *p*-chloromethylbenzylidene diacetate, m. p. 73° (mixed m. p. with original aldehyde, 57—60°) after crystallisation from ligroin (b. p. 40—60°) (Found : C, 56·9; H, 5·2; Cl, 13·35. Calc. for $C_{12}H_{13}O_4Cl$: C, 56·15; H, 5·1; Cl, 13·8%). Again some reaction with side-chain chlorine seems to have taken place. The aldehyde was oxidised with potassium permanganate to *p*-chloromethylbenzoic acid, m. p. 199°, after crystallisation from water.

m-*Chloromethylbenzaldehyde*. A similar technique was used with *m*-chloromethylbenzonitrile, m. p. 68°; the supernatant ether was removed from the precipitated aldimine stannichloride through an inverted sintered-glass filter. After being twice washed *in situ* with dry ether the stannichloride was freed from ether and hydrogen chloride in a vacuum-desiccator and decomposed with warm water, and the aldehyde was repeatedly extracted with ether. The combined ether extracts were repeatedly washed with sodium hydrogen carbonate, and the residue from the dried (Na_2SO_4) ether solution was distilled (N_2 stream) (b. p. 76—77°/0·3 mm.). Redistillation (N_2) just before use gave the aldehyde, b. p. 64·5°/0·13 mm., which was collected in a previously degassed receiver and sealed under nitrogen. In spite of all precautions this aldehyde is very rapidly oxidised to *m*-chloromethylbenzoic acid, m. p. 135° after crystallisation from water (Reinglass [24] gives m. p. 135°) and hence is difficult to analyse (Found : C, 63·0; H, 4·4; Cl, 23·35. Calc. for C_8H_7OCl : C, 62·15; H, 4·6; Cl, 22·9%). It was characterised as its *semicarbazone*, m. p. 213° (from ethanol) (Found : Cl, 17·1; N, 19·8. $C_9H_{10}ON_3Cl$ requires Cl, 16·75; N, 19·85%). The extreme ease of oxidation of this aldehyde made it difficult to manipulate and generally unsuitable as an intermediate for the preparation of other required aldehydes. It was, however, converted into the *m*-methoxymethyl compound.

p-*Hydroxymethylbenzaldehyde*. Attempted hydrolysis of the *p*-chloromethylaldehyde with moist silver oxide caused simultaneous oxidation to *p*-hydroxymethylbenzoic acid, m. p. 178° (raised to 179° by admixture with a genuine specimen, m. p. 180°) after crystallisation from water. A suspension of *p*-chloromethylbenzaldehyde (11 g.) in ~0·005N-barium hydroxide (25 ml.) was refluxed in an atmosphere of nitrogen for 3 hr. After saturation with salt the solution was extracted with ether. The residue from the dried ethereal solution crystallised at 0° to give a white solid, m. p. 39—42° (63%). Attempted distillation of this (N_2) at 160—180°/1·5 mm. gave a glassy polymer which reverted to the original monomeric aldehyde during 6 months. Purification was best effected by crystallisation (repeated Soxhlet extraction) from ligroin (b. p. 40—60°) in which it is only slightly soluble and thus was obtained p-*hydroxymethylbenzaldehyde*, m. p. 47° (Found : C, 70·7; H, 6·0. $C_8H_8O_2$ requires C, 70·6; H, 5·9%). Löw [25] and le Canu [26] describe this compound, prepared from *p*-$CH_2Br{\cdot}C_6H_4{\cdot}CHBr_2$, as a liquid. The same aldehyde was isolated (from the ethereal solution obtained by continuous ether-extraction of the combined aqueous liquors of the Stephen reaction on *p*-chloromethylbenzonitrile) as its (?) cis-2 : 4-*dinitrophenylhydrazone*, m. p. 164° (from alcohol) (Found : C, 52·4; H, 4·1%) and (?) trans-2 : 4-*dinitrophenylhydrazone*, m. p. 232° (mixed m. p. with *cis*-, 182—185°) (Found :

[24] Reinglass, *Ber.*, 1891, **24**, 2418.
[25] Löw, *Annalen*, 1885, **231**, 363.
[26] Le Canu, *Compt. rend.*, 1894, **118**, 535.

C, 52·0; H, 3·9; N, 15·8. $C_{14}H_{12}O_5N_4$ requires C, 53·2; H, 3·8; N, 17·7%), and not depressing the m. p. of the same derivative prepared from the genuine aldehyde.

p-*Bromomethylbenzaldehyde.* Attempts at direct conversion of *p*-chloromethylbenzaldehyde by potassium bromide in hot aqueous alcohol resulted in only partial halogen replacement and some hydrolysis. Introduction of dry bromine (208 g.) under the surface of *p*-tolunitrile (143 g.) at 180° (not at its b. p.) with illumination, afforded *p*-cyanobenzyl bromide (119 g., 50%), m. p. 115—117° after crystallisation from ligroin (b. p. 60—80°). Application of the modified Stephen method to this nitrile was accompanied by complications similar to those observed in the corresponding chloromethyl compound and, in addition, hydrolysis of the aldimine stannichloride yielded a solid, m. p. 82°, which appears to be mixed crystals of the required aldehyde, *p*-hydroxymethylbenzaldehyde, and the original nitrile. Repeated crystallisation from ligroin (b. p. 60—80°) raised the m. p. to 92—94°; subsequent fractional sublimation at 50 mm. gave (*a*) at 70° *p*-hydroxymethylbenzaldehyde, m. p. 38—40° and (*b*) at 100—120° slightly impure *p*-bromomethylbenzaldehyde, m. p. 94—95°. The action of thionyl bromide on *p*-hydroxymethylbenzaldehyde under reflux caused oxidation, giving *p*-bromomethylbenzoic acid, m. p. and mixed m. p. 223°, and, at 30—40°, a solid, m. p. 117—118°, which is probably impure ωω'ω'-tribromo-*p*-xylene (le Canu [26] gives m. p. 116°) (Found: C, 28·7; H, 3·3; Br, 68·9. Calc. for $C_8H_7Br_3$: C, 28·0; H, 2·0; Br, 70·0%). The best method for preparation of the required aldehyde is to warm *p*-hydroxymethylbenzaldehyde and phosphorus tribromide in dry benzene at 45° for 10 min. After 2 hr. at room temperature the mixture was poured into water, and the separated solid was washed with aqueous sodium hydrogen carbonate and water and dried. Crystallisation fron ligroin (b. p. 40—60°) gave p-*bromomethylbenzaldehyde*, m. p. 96° (Found: C, 48·5; H, 4·0; Br, 40·0. C_8H_7OBr requires C, 48·3; H, 3·55; Br, 40·15%).

p-*Iodomethylbenzaldehyde.* The *p*-chloromethyl-aldehyde was heated under reflux with potassium iodide in dry acetone for 30 hr.; the solvent was distilled off and the residue was extracted with ether. Concentration of this solution gave p-*iodomethylbenzaldehyde* as yellow flakes, m. p. 118° (63%), identical with a specimen prepared by the action of an excess of phosphorus tri-iodide on *p*-hydroxymethylbenzaldehyde in benzene at 50° for 1 hr. (Found: C, 38·8; H, 2·6; I, 51·2. C_8H_7OI requires C, 39·05; H, 2·9; I, 51·6%). Preparation of this aldehyde by the Stephen method from *p*-cyanobenzyl iodide, m. p. 144° (from the chloro-compound and potassium iodide in dry acetone), failed.

p-*Methoxymethylbenzaldehyde.* This has previously [27] been prepared by methods different from that used by us. A solution of sodium (1·197 g.) in dry methyl alcohol (50 ml.) was added in small portions during 6—8 hr. to a solution of *p*-chloromethylbenzaldehyde (8·065 g.) in the same solvent (100 ml.) heated in nitrogen under reflux. The mixture was allowed to regain neutrality (phenolphthalein) after each addition of sodium methoxide. Then the solution was concentrated and poured into a 4-fold excess of semicarbazide hydrochloride in saturated sodium acetate solution. The purified semicarbazone, m. p. 184° (from alcohol) (Sabetay [27b] gives m. p. 186°) (Found: C, 57·8; H, 6·2; N, 20·4. Calc. for $C_{10}H_{13}O_2N_3$: C, 57·95; H, 6·3; N, 20·3%), was steam-distilled (CO_2 stream) with oxalic acid solution. The distillate was saturated with salt and extracted with ether. Distillation (N_2) of the residue from the dried ethereal solution gave the required aldehyde, b. p. 129°/18 mm. (overall yield, 52%) (Found: C, 71·6; H, 6·9. Calc. for $C_9H_{10}O_2$: C, 72·0; H, 6·7%). Oxidation with cold, neutral potassium permanganate converted it into *p*-methoxymethylbenzoic acid, m. p. 120—122° (Quelet [27a] gives m. p. 123°).

m-*Methoxymethylbenzaldehyde.* (*a*) *m*-Chloromethylbenzonitrile (9·3 g.) in dry methyl alcohol (65 ml.) was heated under reflux with a solution of sodium (1·41 g.) in the same solvent (25 ml.) until neutral (3—4 hr.). Water (20 ml.) was added to dissolve the precipitated salt, most of the methyl alcohol was removed by distillation, and the residue was extracted with ether, whence distillation of the product gave *m*-methoxymethylbenzonitrile [28] (7·6 g.), b. p. 132°/14 mm. (Found: C, 73·3; H, 6·1; N, 9·9. Calc. for C_9H_9ON: C, 73·4; H, 6·1; N, 9·5%). By Stephen's method this gave a product, b. p. 85—86°/0·4 mm., which, by determination as the 2 : 4-dinitrophenylhydrazone, contained only ~35% of the aldehyde. This was isolated with aqueous sodium hydrogen sulphite from which was regenerated m-*methoxymethylbenzaldehyde*, b. p. 76·5°/0·35 mm. (Found: C, 72·4; H, 6·6. $C_9H_{10}O_2$ requires C, 72·0; H, 6·7%). Its *semicarbazone*, m. p. 184° (from methanol) (Found: C, 57·8; H, 6·5; N, 20·6.

[27] (*a*) Quelet, *Bull. Soc. chim.* (*France*), 1933, **53**, 22; (*b*) Sabetay, *Compt. rend.*, 1931, **193**, 1194; (*c*) Arditti and Palfray, *ibid.*, 1946, **223**, 547.

[28] Cf. Mann and Stewart, *J.*, 1954, 2825.

$C_{16}H_{12}O_2N_2$ requires C, 57·95; H, 6·3; N, 20·3%), regenerated the aldehyde when steam-distilled (N_2) with oxalic acid from saturated brine. The aldehyde is very readily oxidised.

(*b*) *m*-Chloromethylbenzaldehyde, when treated with sodium methoxide as for the *p*-compound, gave the aldehyde, b. p. 68°/0·18 mm.; the m. p. (184°) of the semicarbazone was not depressed on admixture with the sample obtained as above, but admixture depressed the m. p. of the semicarbazone of the *p*-methoxymethylbenzaldehyde to 157—162°.

Ethyl p-*formylphenylacetate.* Some difficulty was experienced in the preparation of this compound. Various methods to replace the side-chain chlorine in the *p*-chloromethyl-aldehyde by the cyano-group failed, gave mainly the hydroxymethyl compound, or (with potassium cyanide) caused a benzoin condensation to give 4 : 4′-*bisethoxymethylbenzoin*, b. p. 82°/1·5 mm. (Found : C, 73·1; H, 7·5. $C_{20}H_{24}O_4$ requires C, 73·1; H, 7·7%). Conditions for the partial hydrolysis of *p*-cyanobenzyl cyanide [29] proved too sensitive to provide a satisfactory method, *p*-carbamidophenylacetic acid, m. p. 229°, being the usual product. The route, *p*-aminophenylacetic acid ⟶ *p*-cyanophenylacetic acid and the application of Stephen's reaction to the ester of the latter was also unsatisfactory. The aldehyde was finally obtained by Sommelet's method [30] but the required experimental conditions for chloromethylation of ethyl phenylacetate with chloromethyl methyl ether and stannic chloride are stringent. At −10° no reaction occurs : at 60—70° or at 25—32° polymers are obtained. Ethyl phenylacetate (104 g.) was added slowly to a stirred mixture of chloromethyl methyl ether (54 g.) and stannic chloride (250 g.), the temperature being kept at 5—10°. The mixture was poured on crushed ice and extracted with ether. The ethereal solution, when washed with aqueous sodium carbonate and dried, gave a pale yellow oil, distillation of which gave unchanged ethyl phenylacetate and ethyl *p*-chloromethylphenylacetate, b. p. 99—110°/0·05 mm. (Found : Cl, 14·6. Calc. for $C_{11}H_{13}O_2Cl$: Cl, 16·7%), containing ethyl *p*-methoxymethylphenylacetate (12—20%). Hydrolysis of the crude product with sodium hydroxide afforded a polymer, m. p. 110—130°, probably a polyester of *p*-hydroxymethylphenylacetic acid. The crude product, b. p. 99—110°/0·05 mm. (121 g.), and hexamine (133 g.) were heated in 50% acetic acid (1200 ml.) at 90° for 4 hr. in an atmosphere of carbon dioxide.[31] The solution was neutralised with solid sodium carbonate (700 g.) and extracted with ether. The solution was shaken with sodium hydrogen sulphite (375 g. in 600 ml. of water), and the bisulphite compound was filtered off and washed with ether. A further quantity was obtained by re-saturation of the aqueous filtrate. The ethereal washings and extract of the filtrate gave *ethyl* p-*methoxymethylphenylacetate*, b. p. 104—108°/0·05 mm. (Found : C, 69·0; H, 8·2. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·75%). The aldehyde bisulphite compound was decomposed with cold, aqueous sodium carbonate and extracted with ether. Some polymerisation occurred when the residue from the dried ethereal extract was distilled but 65% distilled at 97—110°/0·06 mm. and, when kept sealed under nitrogen for 12 hr. at 0°, crystallised. Filtration at 4° and redistillation of the separated crystals at 104—108°/0·05 mm. gave the aldehyde, m. p. 34—36°. Various methods of purification, including regeneration from its semicarbazone, were unsuccessful and it was best purified by rapid distillation (N_2) at 105°/0·05 mm. The distillate solidified to give pure *ethyl* p-*formylphenylacetate*, m. p. 38° (Found : C, 69·1; H, 6·3. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·3%). The overall yield of pure compound was 12—14%. The aldehyde is readily oxidised and was kept sealed under nitrogen. It was characterised as its *semicarbazone*, m. p. 182° (from absolute alcohol) (Found : C, 57·5; H, 6·0; N, 16·8. $C_{12}H_{15}O_3N_3$ requires C, 57·8; H, 6·1; N, 16·9%), and 2 : 4-dinitrophenylhydrazone, m. p. 134—136°. Oxidation with boiling aqueous potassium permanganate afforded terephthalic acid, identified as its dimethyl ester, m. p. and mixed m. p. 139—140°.

p-*Formylphenylacetic acid.* The ester (5 g.) was refluxed under carbon dioxide with a slight excess of a 1% solution of sodium hydrogen carbonate until dissolved (3 hr.). The acidified solution was extracted with ether. Concentration of the dried ether solution gave the *acid* as pale yellow needles, m. p. 131° (Found : C, 65·9; H, 5·1. $C_9H_8O_3$ requires C, 65·9; H, 4·9%) but in all subsequent crystallisations, as colourless prisms, m. p. and mixed m. p. 131° (Found : C, 65·65; H, 5·2%). In equilibration experiments the required potassium salt was prepared by neutralisation of the acid with a standard solution of potassium hydroxide in constant-boiling alcohol.

Methyl m-*formylphenylacetate.*—Many attempts to prepare this compound only produced sufficient product to characterise it as its *semicarbazone*, m. p. 195° (from methyl alcohol) (Found :

[29] Mellinghoff, *Ber.*, 1889, **22**, 3209.
[30] Sommelet, *Compt. rend.*, 1913, **157**, 1443.
[31] Cf. Angyal and Rassack, *J.*, 1949, 2700; 1950, 2141.

C, 56·4; H, 5·6; N, 18·2. $C_{11}H_{12}O_2N_2$ requires C, 56·2; H, 5·6; N, 17·9%). *m*-Nitrobenzyl chloride was converted through the nitrile into *m*-nitrophenylacetic acid which was reduced [32] to *m*-aminophenylacetic acid. The unpurified acid, m. p. 164—148°, was converted by the Sandmeyer reaction into *m*-cyanophenylacetic acid, m. p. 114° (Found: C, 67·2; H, 4·5. Calc. for $C_9H_7O_2N$: C, 67·1; H, 4·35%), the *methyl ester*, b. p. 100·5°/0·15 mm. (Found: C, 68·5; H, 5·2; N, 8·3. $C_{10}H_9O_2N$ requires C, 68·5; H, 5·2; N, 8·0%), of which was prepared by the silver salt method. Erratic results were obtained when the Stephen method was applied to this ester but in one small-scale experiment a small amount of the aldehyde was obtained from which the semicarbazone was prepared. Attempts to convert *m*-cyanophenylacetic acid into the *m*-aldehyde by Stephen's method failed, and Beech's method [33] applied to *m*-aminophenylacetic acid gave only a trace of water-soluble aldehyde which, converted through its silver salt, gave the methyl ester, b. p. 104°/0·05 mm., the semicarbazone of which was identical with that prepared above.

*Triethyl-*p*-formylbenzylammonium chloride.* Equimolar quantities of *p*-chloromethylbenzaldehyde (5·2 g.) and triethylamine (3·6 g.) with a few ml. of alcohol were sealed together and kept at 60° for 1 week. The separated salt was washed with 96% alcohol, the solution concentrated, and benzene was added. All water was removed by azeotropic distillation with fresh additions of dry benzene. The residual yellow oil crystallised and was kept sealed under dry benzene at 0° for 5 days. The crystals were drained on porous pot and the hygroscopic *salt* was dried and stored in a desiccator over phosphoric oxide (Found: C, 65·0; H, 9·0; N, 5·55; Cl, 13·8. $C_{14}H_{22}ONCl$ requires C, 65·7; H, 8·7; N, 5·5; Cl, 13·9%). The *styphnate* has m. p. 110° (from water) (Found: C, 50·7; H, 4·7; N, 11·65. $C_{20}H_{24}O_9N_4$ requires C, 51·7; H, 5·2; N, 12·1%).

Equilibrium Determinations.—Except where certain modifications were necessary (p. 405) the equilibrium constants were determined by the microtechnique described in previous Parts of this series, but, instead of removal of silver cyanide by filtration before back-titration of the excess of silver nitrate with standard ammonium thiocyanate, interference due to its solubility was prevented by addition of 5 ml. of pure nitrobenzene to the titration mixture. With all solid aldehydes, the absence of surface oxidation of the crystals was confirmed by examination under a high-power microscope both in ordinary and polarised light. The authors are indebted to Mr. P. Markey of the Department of Physical Chemistry for such examinations.

With *p*-chloromethylbenzaldehyde, under equilibration conditions, quaternary salt formation with the tri-*n*-propylamine catalyst corresponded to only 0·009 ml. of 0·0495N-silver nitrate, equivalent to the removal of only ~3% of the catalyst and well below the estimated titration error of 0·02 ml. The degree of interaction between side-chain chlorine and silver nitrate under the conditions of the determination of the excess of hydrogen cyanide varied slightly with the excess of silver nitrate present and was increased by precipitated silver cyanide. Under the standard conditions used (excess of silver nitrate equiv. to approx. 2·5 ml. of 0·05017N-ammonium thiocyanate; titration completed in 3 min. from the removal of the sample from the equilibrium mixture) a correction of 7·35% was needed, to be added to the back-titre of ammonium thiocyanate to compensate for the reaction of side-chain chlorine. Similar correction was made in determination of the equilibrium value for *m*-chloromethylbenzaldehyde.

Owing to removal of the catalyst, the slow equilibration of *p*-formylphenylacetic acid was followed by determination of the "equilibrium" value over a period of 13·5 weeks (duplicate blank titrations of the hydrogen cyanide solution being made for each reading) with the following results:

Time (weeks)	3	4	5	6	9	10	11	12	13·5
10^3K (mole l.$^{-1}$) (1)	9·22	7·12	7·02	6·30	6·44	4·17	4·03	3·40	—
(2)	—	7·72	7·16	6·81	6·79	5·93	5·92	4·44	2·34

The value of 10^3K was plotted against time and the portion of the curve (6—9 weeks) over which the value of K remained approximately constant was extrapolated to zero time to give the values: 10^3K = 6·43, 6·85; mean, 6·64 ± 0·2 mole l.$^{-1}$.

One of us (J. A. L. B.) thanks the British Council for a post-graduate scholarship to the United Kingdom, and another (D. G. S.) thanks the Ministry of Education for a maintenance award.

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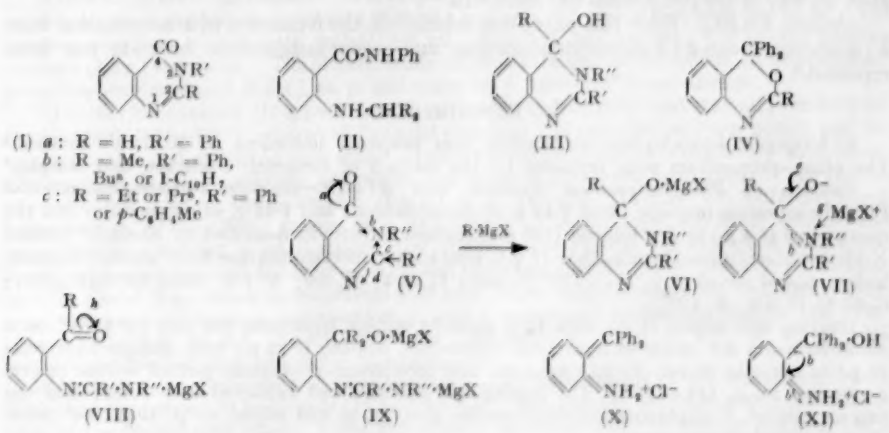
[32] Cf. *Org. Synth.*, Coll. Vol. I, 2nd Edn., p. 52.
[33] Beech, *J.*, 1954, 1297.

82. *Reactions of Substituted 3 : 4-Dihydro-4-oxoquinazolines with Grignard Reagents.*

By I. K. Kacker and S. Husain Zaheer.

Condensation of 3-aryl-3 : 4-dihydro-4-oxoquinazolines with Grignard reagents yields *N*-substituted anthranilamides, but the 2-ethyl or 2-*n*-propyl derivatives give benzoxazine derivatives and the arylamine.

Koelsch [1] reported that 3 : 4-dihydro-4-oxo-3-phenylquinazoline (I*a*) and benzylmagnesium chloride yield *N*-α-benzylphenethylanthranilanilide (II; R = CH_2Ph) and explained its formation by postulating that an electrophilic centre is possible only at position 2 in (I*a*). Sen *et al.*[2] reported the formation of 2 : 3 : 4-trisubstituted 3 : 4-dihydro-4-hydroxyquinazolines (III) by the reaction of the quinazoline derivatives (I*b*) with alkyl- or aryl-magnesium halides and postulated a normal Grignard reaction at the carbonyl group with exclusion of an electrophilic centre at position 2 when it bore a methyl substituent. In our experiments, phenylmagnesium bromide and the compound (I*a*) yielded *N*-(diphenylmethyl)anthranilanilide (II; R = Ph). With its 2-methyl derivative most of the starting material was recovered, but there was obtained a small quantity of a product which was not an anthranilamide or a benzoxazine. Re-examination of the product described by Sen *et al.* as 4-hydroxy-2-methyl-3 : 4-diphenylquinazoline (III; R = R″ = Ph) showed it to be only the hydrochloride of the starting quinazoline. Phenylmagnesium bromide reacted with the 3-aryl-2-ethyl or 3-aryl-2-*n*-propyl derivatives (I*c*) to yield the 4 : 4-diphenyl-



3 : 1 : 4-benzoxazines (IV; R = Et or Pr^n) and aniline or *p*-toluidine. After reaction of these quinazolines and alkylmagnesium halides, most of the starting material was recovered, with a little aniline or *p*-toluidine.

Hydrolysis of the anthranilamide (II; R = Ph) with sodium hydroxide in ethylene glycol yielded aniline and *N*-(diphenylmethyl)anthranilic acid. The latter was synthesised by treating anthranilic acid with diphenylmethyl chloride in pyridine and conversion of the product into its anilide.

Alcoholic alkali converted the benzoxazines (IV; R = Et or Pr^n) into *o*-aminophenyldiphenylmethanol (prepared also by Baeyer and Villiger's method [3]); hot hydrochloric acid yielded, in addition, benzophenone and aniline. Treating the first of these products with propionic and butyric anhydride gave the benzoxazines (IV; R = Et or Pr^n),

[1] Koelsch, *J. Amer. Chem. Soc.*, 1945, **67**, 1718.
[2] Sen *et al.*, *J. Indian Chem. Soc.*, 1948, **25**, 437; 1950, **27**, 40.
[3] Baeyer and Villiger, *Ber.*, 1904, **37**, 3192.

whether or not fused sodium acetate was also added. However, we confirmed Baeyer and Villiger's finding [3] that acetylation in absence of fused sodium acetate leads to *o*-acetamidophenyldiphenylmethanol, while presence of fused sodium acetate leads to the 3 : 1 : 4-benzoxazine derivative (IV; R = Me). Treatment of this with hydrochloric or acetic acid opens the ring (cf. Baeyer and Villiger [3]). When R is ethyl or *n*-propyl, the 2-acylaminophenyldiphenylmethanol produced rapidly cyclises again to the benzoxazine.

Thus the reaction of these substituted quinazolines with Grignard reagents depends on the nature of the 2-substituent. When there is no 2-substituent an electrophilic centre develops there and not at position 4, and the reaction proceeds as described by Koelsch.[1] With a 2-ethyl or 2-*n*-propyl substituent the predominant electrophilic centre is at position 4, and leads to formation of a 3 : 1 : 4-benzoxazine derivative and an aromatic amine. This may be explained as follows.

Polarisations *a* and *b* (cf. V) create a strong electrophilic centre at position 4, but polarisation *d*, helped by process *c*, tends to produce electron-deficiency at position 2, which is counteracted by the electron-feeding property of the entrant group R′ (Et or Pr^n). Hence the normal 1 : 2-addition of R^-MgX^+ takes place at the carbonyl group, giving rise to the compound (VI). MgX^+ is then split off from this, yielding structure (VII), wherein processes *e*, *f*, and *g* assist to form (VIII) which is a more stable form. Addition of a second molecule of R·MgX across the carbonyl group (assisted by process *h*) gives the material (IX), which in turn yields the benzoxazine (IV) with the elimination of $R''{\cdot}N(MgX)_2$.

The benzophenone and aniline obtained in small amount on acid hydrolysis of the benzoxazines (IV) are also obtained on prolonged treatment of the primary products, *o*-aminophenyldiphenylmethanols, with acid (cf. Baeyer and Villiger [3]). They doubtless arise by way of the compounds (X) and (XI).

[Added, 9.9.55.] Since this paper was submitted, the formation of a benzoxazine from 3 : 4-dihydro-4-oxo-2 : 3-diphenylquinazoline and phenylmagnesium bromide has been reported.[4]

Experimental

2 : 3-Dihydro-4-oxo-3-phenylquinazoline was prepared according to Koelsch's method.[1] The other quinazolines were prepared by the method of Grimmel, Guenther, and Morgan.[5]

Reaction of Phenylmagnesium Bromide with 3 : 4-Dihydro-4-oxo-3-phenylquinazoline.—Phenylmagnesium bromide (from 9·42 g. of bromobenzene and 1·44 g. of magnesium) and the quinazoline (4·4 g.) in dry toluene (100 ml.), caused to react as described by Koelsch,[1] yielded *N*-(diphenylmethyl)anthranilanilide (7 g.), which after recrystallisation from alcohol–benzene, had m. p. and mixed m. p. 174—176° (Found: C, 82·4; H, 5·9; N, 7·4. Calc. for $C_{26}H_{22}ON_2$: C, 82·5; H, 5·9; N, 7·4%).

Heating this anilide (1 g.) with 10% aqueous sodium hydroxide (10 ml.) for 12 hr. on a water-bath did not result in hydrolysis. However, heating it (2 g.) with sodium hydroxide (2 g.) in ethylene glycol (20 ml.) for 1 hr. and then steam-distillation yielded aniline (acetyl derivative, m. p. 114—115°). The residue was acidified and extracted with ether; and the extract yielded *N*-(diphenylmethyl)anthranilic acid, m. p. and mixed m. p. 192—194° (from alcohol) (purple fluorescence).

N-(Diphenylmethyl)anthranilic Acid.—Anthranilic acid (6·8 g.), diphenylmethyl chloride (10·1 g.), and pyridine (1 ml.) were heated on a steam-bath for 15 min., then triturated with dilute hydrochloric acid, and the separated solid was collected, dissolved in dilute sodium hydroxide solution, and reprecipitated with hydrochloric acid. Recrystallisation from alcohol (purple fluorescence) yielded the pale yellow substituted *acid* (10 g., 66%), m. p. 192—194° (Found: C, 79·0; H, 5·6; N, 4·5. $C_{20}H_{17}O_2N$ requires C, 79·2; H, 5·7; N, 4·6%).

With thionyl chloride, followed by aniline, this gives the pale yellow *anilide* (from alcohol–benzene), m. p. 174—176° (Found: C, 82·1; H, 6·1; N, 7·1%).

Reaction of Phenylmagnesium Bromide with 2-Ethyl-3 : 4-dihydro-4-oxo-3-phenylquinazoline.—To a well-stirred solution of phenylmagnesium bromide (from bromobenzene, 31·4 g., and magnesium, 4·8 g.) in ether (150 ml.), cooled in ice–salt, was added dropwise a solution of the quinazoline (25 g.) in benzene (100 ml.). The mixture was then refluxed for 6 hr. and poured on

[4] Mustafa, Asker, Kamel, Shalaby, and Hassan, *J. Amer. Chem. Soc.*, 1955, **77**, 1612.
[5] Grimmel, Guenther, and Morgan, *ibid.*, 1946, **68**, 542; cf. Zaheer and Kacker, *J. Indian Chem. Soc.*, 1951, **28**, 344.

crushed ice; ammonium chloride was added. The solvent layer was dried (Na_2SO_4) and the solvents were removed. From the dark red viscous residue, by the addition of a little alcohol and prolonged cooling, a solid (13·5 g.) was obtained, which on recrystallisation from alcohol–benzene, gave colourless crystals (B), m. p. 154—155°. The mother-liquors slowly gave a further 2·6 g. By extracting the combined mother-liquors with dilute hydrochloric acid, aniline (5·6 g.) was isolated. The solvent layers, after acid-extraction, yielded small quantities of the starting quinazoline and of diphenyl.

In an alternative method of working up, the solvent layer, after decomposition of the complex, was steam-distilled, and from the viscous residue, by working up with a little alcohol, the compound B (25 g.) was isolated. Recrystallised as before, this melted at 154—155°. From the steam-distillate, aniline (6·5 g.) was obtained. The benzoxazine (B) yielded a picrate, m. p. 186—187°, a picrolonate, m. p. 177—178° (decomp.), and did not depress the m. p. of 2-ethyl-4 : 4-diphenyl-3 : 1 : 4-benzoxazine (Found : C, 84·4; H, 6·2; N, 4·7%; *M*, 315. $C_{23}H_{19}ON$ requires C, 84·3; H, 6·1; N, 4·5%; *M*, 313·4).

Reaction of Phenylmagnesium Bromide with 2-*Ethyl*-3 : 4-*dihydro*-4-*oxo*-3-p-*tolylquinazoline.*—This reaction, carried out as in the previous experiment (quinazoline, 26·4 g., in dry benzene, 150 ml.), yielded the crystalline oxazine (26 g.) obtained in the previous experiment. *p*-Toluidine (6·8 g.) (acetyl derivative, m. p. 146°) was also obtained.

Reaction of Phenylmagnesium Bromide with 3 : 4-*Dihydro*-4-*oxo*-3-*phenyl*-2-n-*propylquinazoline.*—Bromobenzene (6·28 g.), magnesium (0·96 g.), and this quinazoline (5·28 g.), in benzene (80 ml.) gave aniline and 4 : 4-diphenyl-2-*n*-propyl-3 : 1 : 4-benzoxazine (3 g.), m. p. and mixed m. p. 156—157° (from alcohol) (Found : C, 84·3; H, 6·5; N, 4·2%; *M*, 327. $C_{23}H_{21}ON$ requires C, 84·4; H, 6·5; N, 4·3%; *M*, 327·4).

3 : 4-Dihydro-4-oxo-2-*n*-propyl-3-*p*-tolylquinazoline (5·5 g.) gave *p*-toluidine and the same benzoxazine (2·5 g.).

Hydrolysis of the Benzoxazines.—(*a*) A suspension of either of the preceding benzoxazines (2 g.) in 10% alcoholic potassium hydroxide (100 ml.) was refluxed on a steam-bath for 16 hr. The mixture was then treated with water (200 ml.), acidified, and cooled. Unchanged starting material (1·2 g.) separated. The filtrate, made alkaline with sodium carbonate, yielded *o*-aminophenyldiphenylmethanol (0·2 g.), m. p. and mixed m. p. 120—121° (from alcohol).

(*b*) Either benzoxazine (10 g.) was heated with 15% hydrochloric acid (150 ml.) for 4—5 hr. in an oil-bath (120—130°); almost all the solid dissolved. Water (250 ml.) was added, and the mixture cooled and extracted with ether. The ether extract, washed successively with water, dilute sodium carbonate solution, and water, was dried (Na_2SO_4), and evaporated. The residue on distillation yielded benzophenone (4·1 g.), b. p. 185—190°/15 mm. (2 : 4-dinitrophenylhydrazone, m. p. 235—236°; oxime, m. p. 142—143°). The acid layer was made alkaline and steam-distilled, yielding a small quantity of aniline. The residue was extracted with ether, most of the ether removed from the extract, and hydrogen chloride passed through the residue, yielding a solid (2 g.) which on trituration with cold dilute aqueous ammonia and recrystallisation from alcohol had m. p. and mixed m. p. with *o*-aminophenyldiphenylmethanol, 121—122° (Found : C, 82·8; H, 6·4; N, 5·1. Calc. for $C_{19}H_{17}ON$: C, 82·9; H, 6·2; N, 5·1%). Its acetyl derivative had m. p. and mixed m. p. 196—197°.

Hydrolysis of o-Aminophenyldiphenylmethanol.—(*a*) The alcohol (1 g.) was heated with 10% alcoholic potassium hydroxide (15 ml.) for 6 hr., then diluted, acidified with hydrochloric acid, and extracted with ether. From the extract, on removal of the ether, a few drops of a brown liquid were obtained, which did not give the usual test for a keto-group. The residue from the ether-extraction was made alkaline with ammonia; the unchanged alcohol (0·8 g.) was recovered.

(*b*) After hydrolysis of 1 g. with 15% hydrochloric acid (12 ml.) as described for the benzoxazines most of the starting material was recovered, but small quantities of aniline and benzophenone were identified.

2-*Ethyl*-4 : 4-*diphenyl*-3 : 1 : 4-*benzoxazine.*—*o*-Aminophenyldiphenylmethanol (0·5 g.), propionic anhydride (3 ml.), and fused sodium acetate (0·5 g.) were heated together for 30 min. on a steam-bath. Working up as usual gave the *benzoxazine* (0·3 g.), m. p. 144—145° (from alcohol–benzene) (also obtained if the sodium acetate was omitted) (Found : C, 84·2; H, 6·0; N, 4·5. $C_{23}H_{19}ON$ requires C, 84·3; H, 6·1; N, 4·5%).

4 : 4-*Diphenyl*-2-n-*propyl*-3 : 1 : 4-*benzoxazine.*—*o*-Aminophenyldiphenylmethanol (0·5 g.) and *n*-butyric anhydride (3 ml.), with or without fused sodium acetate, treated as above, yielded 0·2 g. of this *benzoxazine*, m. p. 156—157° (from alcohol) (Found : C, 84·4; H, 6·2; N, 4·3. $C_{23}H_{21}ON$ requires C, 84·4; H, 6·5; N, 4·5%).

Attempted Preparation of Diphenyl-o-propionamidophenylmethanol.—(*a*) Hydrogenchloride was passed through a cooled solution of 2-ethyl-4 : 4-diphenylbenzoxazine (2 g.) in ether–benzene (20 ml.), a solid separating. This, on filtration and washing with ether, had m. p. 185—189° (decomp.). On recrystallising from alcohol, the m. p. was lowered and after three recrystallisations the benzoxazine was regenerated (m. p. 154—155°).

(*b*) A solution of the benzoxazine (1 g.) in glacial acetic acid (8 ml.) was heated on a steam-bath for 1 hr. It was then poured on crushed ice, and the separated solid filtered off. This melted at 190—195° (decomp.) but behaved similarly to the product obtained as in (*a*).

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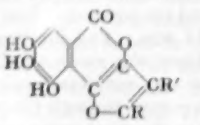
83. *Galloflavin. Part III.* The Position of the Carboxyl Group in isoGalloflavin and a Synthesis of Trimethylbrevifolin.*

By JAMES GRIMSHAW and ROBERT D. HAWORTH.

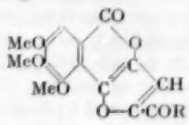
The correctness of structure (I) for *iso*galloflavin has been proved by conversion of trimethyl*iso*galloflavin into 5 : 6 : 7-trimethoxy-5′-*n*-propylfurano-(3′ : 2′-3 : 4)*iso*coumarin, which yielded 3-acetyl-4 : 5 : 6-trimethoxyphthalide, 4 : 5 : 6-trimethoxyphthalide-3-carboxylic acid, methyl *n*-propyl ketone, and *n*-butyric acid.

A synthesis of tri-*O*-methylbrevifolin from 5 : 6 : 7-trimethoxy-4-*iso*coumarinylacetic acid has also been realised.

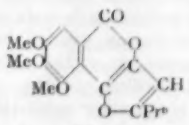
PREVIOUS work * led to the conclusion that *iso*galloflavin, obtained by the action of alkali on galloflavin, had either structure (I) or structure (II); experiments now reported have enabled a decision to be made in favour of structure (I). These involved conversion of the carboxyl group of tri-*O*-methyl*iso*galloflavin (III; R = OH) into an *n*-propyl group. The product (IV) proved, as expected, unstable to alkali and identification of the hydrolysis products revealed the structure of *iso*galloflavin.



(I) : R = CO_2H, R′ = H
(II) : R = H, R′ = CO_2H



(III)



(IV)

The relatively large amounts of tri-*O*-methyl*iso*galloflavin were obtained, without recourse to diazomethane, by methylating the methyl ester with methyl sulphate and potassium carbonate in acetophenone and then hydrolysing the ester group. Galloflavin was similarly tetramethylated in xylene, although Herzig and Wachsler [1] found that methylation in aqueous alkali caused formation of tri- and tetra-methyl derivatives of *iso*galloflavin as well as partial rupture of the *iso*coumarin ring.

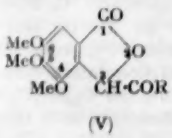
After an unsuccessful attempt to reduce the exocyclic ester but not the lactone group of tetramethyl*iso*galloflavin (III; R = OMe) with lithium aluminium hydride, attention was turned to the acid chloride (III; R = Cl) which was readily formed from trimethyl*iso*galloflavin by thionyl chloride. This chloride did not undergo the Friedel–Crafts reaction with anisole or veratrole, and the derived amide could not be dehydrated. However the chloride was normally hydrolysed to the acid by aqueous acetic acid, and converted into esters and thiolesters by the usual reactions. With diethylcadmium in ether it gave variable yields of 5 : 6 : 7-trimethoxy-5′-propionylfurano(3′ : 2′-3 : 4)*iso*coumarin (III; R = Et), and on one occasion tri-*O*-methyl*iso*galloflavin ethyl ester (III; R = OEt) was

* Parts I and II, *J.*, 1952, 1583; 1955, 833.

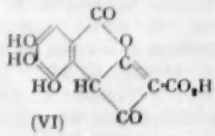
[1] Herzig and Wachsler, *Monatsh.*, 1914, **35**, 77.

the major product, presumably owing to reaction of the chloride with the solvent. Results were however satisfactory when benzene was the solvent.[2]

Clemmensen reduction of the ketone (III; R = Et) afforded the 5′-*n*-propyl derivative (IV), and the low yields obtained were presumably due to the instability of the product to the acidic conditions. The *n*-propyl compound was more stable to alkali than was the decarboxy-compound derived [3] from (I), but when boiled in 5% aqueous-methanolic potassium hydroxide for 4 hr. yielded 3-acetyl-4 : 5 : 6-trimethoxyphthalide (V; R = Me), 4 : 5 : 6-trimethoxyphthalide-3-carboxylic acid (V; R = OH), methyl *n*-propyl ketone, and butyric acid. The formation of the last two products shows that the propyl group must be attached to a carbon atom which bears oxygen. All four products are expected if the propylfurano*iso*coumarin has formula (IV), whence it follows that the intermediate ketone is (III; R = Et) and that *iso*galloflavin has structure (I). On the other hand, the propyl derivative corresponding to the alternative *iso*galloflavin formula (II) would be expected to yield 4 : 5 : 6-trimethoxyphthalide-3-carboxylic acid, 4 : 5 : 6-trimethoxy-3-*n*-valerylphthalide, *n*-valeraldehyde, and formic acid. Herzig's earlier formula [3] (VI) for *iso*galloflavin, previously considered erroneous on the basis of negative evidence and theoretical objections,[4] also fails to account for this new evidence. As a result of this



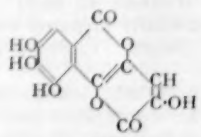
(V)



(VI)

proof of the *iso*galloflavin formula (I) it may be deduced [4] that galloflavin is represented by (VII); a scheme for its formation from gallic acid has previously [5] been proposed. Gilman and Wright [6] have show that the carboxyl group of α- but not of β-furoic acids is replaced by the mercurichloride group when the potassium salt is warmed with mercuric chloride. Tri-*O*-methyl*iso*galloflavin undergoes a similar replacement thus providing additional proof that the carboxyl group occupies an α-position in *iso*galloflavin.

Discussion of the mechanism of the formation of galloflavin led to our interpreting the degradative work of Schmidt and Bernauer [7] on brevifolincarboxylic acid, the major crystalline component of *Algarobilla* tannin, in terms of structure (VIII; R = H, R′ = CO_2H) not previously considered. We have now confirmed the formula proposed by these workers for the derived tri-*O*-methylbrevifolin (VIII; R = Me, R′ = H), by synthesis briefly reported elsewhere.[8] Schmidt and Bernauer [9] have also described a synthesis of tri-*O*-methylbrevifolin by an entirely different route.



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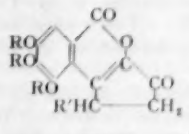
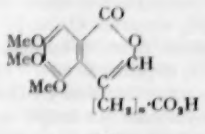


(VIII)



(IX)

5 : 6 : 7-Trimethoxy-4-*iso*coumarinylacetic acid (IX; $n = 1$) [10] gave a diazo-ketone which was rearranged by silver benzoate–triethylamine [11] in methanol to methyl β-(5 : 6 : 7-trimethoxy-4-*iso*coumarinyl)propionate. Acid hydrolysis afforded the corresponding acid (IX; $n = 2$) which was cyclised with phosphorus pentoxide in boiling benzene (cf. Plattner

[2] Cf. Cason and Prout, *J. Amer. Chem. Soc.*, 1944, **66**, 46.
[3] Herzig, *Annalen*, 1920, **421**, 247.
[4] Part I, *J.*, 1952, 1583.
[5] Part II, *J.*, 1955, 833.
[6] Gilman and Wright, *J. Amer. Chem. Soc.*, 1933, **55**, 3302.
[7] Schmidt and Bernauer, *Annalen*, 1954, **588**, 211.
[8] Grimshaw and Haworth, *Chem. and Ind.*, 1955, 199.
[9] Schmidt and Bernauer, *Annalen*, 1955, **591**, 133.
[10] Haworth, Pindred, and Jefferies, *J.*, 1954, 3617.
[11] Newman and Beal, *J. Amer. Chem. Soc.*, 1950, **72**, 5163.

and Pfau [12]) to give good yields of tri-*O*-methylbrevifolin. This and its 2 : 4-dinitrophenylhydrazone were identical with specimens derived from natural sources, kindly supplied by Professor Otto Th. Schmidt.

Experimental

Tetra-O-methylgalloflavin.—Galloflavin (0·5 g.) and anhydrous potassium carbonate (4 g.) were suspended in xylene (20 ml.), and methyl sulphate (1·5 ml.) was added. The mixture was stirred and refluxed gently for 4 hr., then further methyl sulphate (1·5 ml.) was added and the mixture refluxed overnight, cooled, and poured into dilute hydrochloric acid. The xylene was removed in steam, and the residual solid collected and crystallised from acetic acid, giving tetra-*O*-methylgalloflavin (0·3 g.), m. p. and mixed m. p. 236—237°.

Tetra-O-methylisogalloflavin.—*iso*Galloflavin with boiling methanol (100 parts) containing 1% of sulphuric acid gave the methyl ester, needles, m. p. 300—305° (decomp.) (Herzig [3] gives m. p. 300—305°). This ester (5 g.), anhydrous potassium carbonate (30 g.), acetophenone (130 ml.), and methyl sulphate (15 ml.) were stirred and heated under reflux at 130—140°. Further methyl sulphate (15 ml.) was added after 4 hr. and the mixture heated for a total of 10 hr., cooled, poured into dilute hydrochloric acid, diluted with light petroleum (b. p. 80—120°) (50 ml.), and filtered. The residue of almost pure tetra-*O*-methyl*iso*galloflavin (4 g.) crystallised from toluene as needles, m. p. 231—232° (Found : C, 57·6; H, 4·3. Calc. for $C_{16}H_{14}O_8$: C, 57·5; H, 4·2%). Alkaline hydrolysis (cf. Herzig and Wachsler [1]) afforded tri-*O*-methyl*iso*galloflavin as needles, m. p. 264—265° (from 50% acetic acid) (Found : C, 56·7; H, 3·7. Calc. for $C_{15}H_{12}O_8$: C, 56·3; H, 3·8%). Decarboxylation then gave the compound, m. p. 130—132° (Part I) (Found : C, 61·3; H, 4·7. Calc. for $C_{14}H_{12}O_6$: C, 60·9; H, 4·3%). The m. p. of these compounds were undepressed on admixture with those prepared by using diazomethane for the methylation of *iso*galloflavin.

Tri-O-methylisogalloflavin Acid Chloride.—Tri-*O*-methyl*iso*galloflavin, refluxed with thionyl chloride (20 parts) for 2 hr., yielded the *acid chloride*, yellow needles, m. p. 217—218° (from toluene) (Found : C, 53·6; H, 3·6. $C_{18}H_{11}O_7Cl$ requires C, 53·2; H, 3·3%). The acid chloride was dissolved in hot acetic acid and water added at the b. p. until precipitation commenced; trimethyl*iso*galloflavin, m. p. and mixed m. p. 264—265°, which separated was converted by ethereal diazomethane into tetra-*O*-methyl*iso*galloflavin, m. p. and mixed m. p. 231—232°. Decomposition of the acid chloride with methanol furnished the same methyl ester, m. p. and mixed m. p. 231—232° (Found : C, 57·7; H, 4·0%).

The acid chloride with aqueous ammonia (*d* 0·88) gave the *amide* (III; R = NH_2), needles (from 50% acetic acid), m. p. 258—259° (Found : C, 56·5; H, 4·1; N, 4·1. $C_{15}H_{13}O_7N$ requires C, 56·4; H, 4·0; N, 4·4%). This was recovered unchanged after 4 hours' refluxing with thionyl chloride. Phosphoric oxide in toluene (8 hr.) caused much charring and only unchanged amide was recovered.

The acid chloride, dissolved in a minimum of hot ethanol, gave, on cooling, the *ethyl ester* which recrystallised from ethanol in needles, m. p. 170—171° (Found : C, 58·9; H, 4·8. $C_{17}H_{16}O_8$ requires C, 58·7; H, 4·7%). The n-*butyl ester* was similarly prepared with, and crystallised from, *n*-butanol, forming needles, m. p. 129—130° (Found : C, 60·8; H, 5·45. $C_{19}H_{20}O_8$ requires C, 60·6; H, 5·3%).

The chloride from tri-*O*-methyl*iso*galloflavin (0·2 g.), in dioxan (20 ml.), was treated with trimethylamine (10 drops) and ethanethiol (10 drops). During 8 hr. a precipitate was formed. The mixture was then poured into water. The resulting precipitate was dried, dissolved in hot benzene, and filtered. Addition of hot light petroleum (b. p. 60—80°) yielded the *ethyl thiolester* which recrystallised from benzene–light petroleum (b. p. 60—80°) as pale yellow needles, m. p. 166—167° (Found : C, 56·4; H, 4·6. $C_{17}H_{16}O_7S$ requires C, 56·1; H, 4·4%).

5 : 6 : 7-*Trimethoxy-5'-propionylfurano*(3' : 2'-3 : 4)*isocoumarin* (III; R = Et).—Anhydrous cadmium chloride (4·7 g.) was added to the ice-cold reagent from magnesium (1·2 g.) and ethyl bromide (5·5 g.) in ether (50 ml.) (cf. Gilman and Nelson [13]) and stirred for 0·5 hr. The ether was then removed under nitrogen and thiophen-free benzene (40 ml.) added to the residue which was again distilled almost to dryness. Further benzene (40 ml.) was added and the residual cake thoroughly extracted by refluxing and stirring under nitrogen. Half the resulting diethylcadmium solution was added to tri-*O*-methyl*iso*galloflavin acid chloride (3·5 g.) in hot benzene (150 ml.) and after the initial reaction had subsided the mixture was stirred and refluxed under

[12] Plattner and Pfau, *Helv. Chim. Acta*, 1937, **20**, 1474.
[13] Gilman and Nelson, *Rec. Trav. chim.*, 1936, **55**, 518.

nitrogen for 2 hr. On cooling, the bright red mixture was decomposed with ice and dilute hydrochloric acid and diluted with chloroform, and the organic layer was separated and dried. Evaporation of the solvents left a red solid which was refluxed with acetone (80 ml.) and water (40 ml.) for 1 hr.; then water was added and the acetone removed. The residue was extracted with chloroform, and the chloroform extract washed with sodium hydrogen carbonate solution and water and dried (Na_2SO_4). Evaporation left an oil which crystallised on dilution with methanol. This crystalline *ketone* recrystallised from butan-1-ol as needles (0·75 g.), m. p. 201—203°, raised to m. p. 207—208° after several recrystallisations from ethanol (Found: C, 61·0; H, 5·0. $C_{17}H_{16}O_7$ requires C, 61·4; H, 4·8%). Acidification of the carbonate extract gave tri-*O*-methyl*iso*galloflavin (0·5 g.). The ketone in hot methanol gave an insoluble deep red precipitate with Brady's reagent. The p-*nitrophenylhydrazone* crystallised from acetic acid as orange plates, m. p. 281—282° (decomp.) (Found: C, 59·7; H, 4·55; H, 9·35. $C_{23}H_{21}O_9N_3$ requires C, 59·1; H, 4·5; N, 9·0%).

5 : 6 : 7-*Trimethoxy-5'*-n-*propylfurano*(3' : 2'-3 : 4)*iso*coumarin (IV).—The above ketone (0·7 g.) was dissolved in toluene (15 ml.) and refluxed with amalgamated zinc needles (5 g.), water (15 ml.), and concentrated hydrochloric acid (1·5 ml.), further acid (1 ml.) being added every hour. After 10 hr., the mixture was diluted with chloroform and water, and the separated organic layer was washed with sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and evaporated, finally under reduced pressure. The residual oil gave no reaction with Brady's reagent and was distilled at 190° (bath)/0·05 mm., the distillate solidifying (0·13 g.). The resulting *propyl compound* crystallised from methanol as colourless needles, m. p. 135—136° (Found: C, 63·9; H, 5·8. $C_{17}H_{18}O_6$ requires C, 64·2; H, 5·7%), depressed on admixture with decarboxylated trimethyl*iso*galloflavin, m. p. 130—132°.

Action of Alkali on the Propyl Compound (IV).—The compound (0·09 g.) was heated in methanol (2 ml.) and 10% aqueous potassium hydroxide (2 ml.) for 4 hr., becoming bright red. The mixture was then acidified with dilute sulphuric acid and distilled, about half its volume being collected (distillate A). The residue was diluted with water and extracted with ether. The ethereal extract was washed with sodium hydrogen carbonate solution (extract B) and water and dried (Na_2SO_4). Evaporation of the ether left an oil (0·02 g.), which crystallised under methanol. The solid was dissolved in methanol and Brady's reagent added, to give a yellow precipitate, m. p. 198—200°, crystallising from ethanol as yellow needles, m. p. 202—203° (Found: C, 51·5; H, 3·8. Calc. for $C_{19}H_{18}O_9N_4$: C, 51·1; H, 4·0%) undepressed on admixture with 3-acetyl-4 : 5 : 6-trimethoxyphthalide 2 : 4-dinitrophenylhydrazone, m. p. 202—203° (lit., m. p. 202—203°). Extract B was acidified and extracted with ether. The ethereal solution was dried (Na_2SO_4) and evaporated, leaving an oily solid (0·03 g.) which was esterified with ethereal diazomethane. Evaporation of the solvent left an oil which was taken up in benzene (5 ml.) and filtered through alumina (1 g.). Elution with benzene and evaporation of the solvent left a colourless oil (0·02 g.) which slowly solidified and crystallised from *cyclo*hexane in needles, m. p. 118—119° undepressed on admixture with methyl 4 : 5 : 6-trimethoxyphthalide-3-carboxylate, m. p. 119—120° (lit., m. p. 118—120°). Distillate A had a strong odour of butyric acid. It was made alkaline with ammonia and about half the solution was distilled over (distillate C). The residue was chromatographed on paper, markers of formic, *n*-butyric, and *n*-valeric acid being used, with 95% ethanol containing a little ammonia as developing solvent.[14] One spot only, corresponding to *n*-butyric acid, was detected. The residue did not reduce ammoniacal silver nitrate solution, even on boiling. Distillate C was acidified with hydrochloric acid and added to a solution of 2 : 4-dinitrophenylhydrazine (0·03 g.) in dilute hydrochloric acid. The resulting precipitate was collected after 1 day and crystallised from dilute ethanol as orange needles, m. p. 137—138° undepressed by methyl *n*-propyl ketone 2 : 4-dinitrophenylhydrazone, m. p. 137—138° (lit., m. p. 141°).

Action of Mercuric Chloride on Tri-O-methylisogalloflavin.—Mercuric chloride (0·57 g.) in water (15 ml.) was added to tri-*O*-methyl*iso*galloflavin (0·6 g.) and potassium hydrogen carbonate (0·21 g.) in water (20 ml.) and warmed on the steam-bath for 3 hr. The yellow *chloromercuri-derivative* which gradually separated was collected, dried (Found: C, 33·2; H, 2·7. $C_{14}H_{11}O_6ClHg$ requires C, 32·9; H, 2·2%), and crystallised from dimethylformamide as pale yellow needles, decomp. 255° (Found: C, 34·6; H, 2·6. $C_{14}H_{11}O_6ClHg,\frac{1}{2}C_3H_7ON$ requires C, 34·3; H, 2·7%). This derivative was converted into 5 : 6 : 7-trimethoxyfurano(3' : 2'-3 : 4)*iso*coumarin, m. p. 130—132°, by boiling with 2*N*-hydrochloric acid (25 parts) and methanol (25 parts).

[14] Kennedy and Barker, *Analyt. Chem.*, 1951, **23**, 1033.

4-(3-*Diazo*-2-*oxopropyl*)-5 : 6 : 7-*tri*-O-*methoxy*isocoumarin.—5 : 6 : 7-Trimethoxy-4-*iso*coumarinylacetyl chloride [10] (1·5 g.) was finely powdered and slowly added to 3 mols. of diazomethane in ether (*ca.* 60 ml.). A vigorous effervescence resulted and the pure *diazo-ketone* crystallised as buff needles (1·3 g.), m. p. 140—141° (decomp.), recrystallisable from benzene–light petroleum (b. p. 60—80°) (Found: N, 8·8. $C_{15}H_{14}O_6N_2$ requires N, 8·8%).

Methyl β-(5 : 6 : 7-*Trimethoxy*-4-*isocoumarinyl*)*propionate*.—The above diazo-ketone (1·2 g.), dissolved in cold methanol (70 ml.), was treated with a filtered solution of silver benzoate (0·5 g.) in triethylamine (4 ml.) during 90 min., set aside for 60 min., and then refluxed with charcoal and a little formic acid, filtered, and evaporated somewhat. Dilution of the residue with water precipitated the product which was extracted with ether. The ethereal solution was washed with sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and evaporated, yielding the *methyl ester* (0·69 g.), needles (from methanol), m. p. 97—98° (Found: C, 59·3; H, 5·7. $C_{16}H_{18}O_7$ requires C, 59·6; H, 5·6%).

Refluxing the ester (0·5 g.) for 2 hr. with concentrated hydrochloric acid (4 ml.), acetic acid (1 ml.), and water (1 ml.), gave the *acid*, needles (0·35 g.) (from benzene), m. p. 179—180° (Found: C, 58·0; H, 5·3. $C_{15}H_{16}O_7$ requires C, 58·4; H, 5·2%).

5 : 6 : 7-*Trimethoxy*-5′-*oxo*-3 : 4-cyclo*pentenoisocoumarin* (VIII; R = Me, R′ = H).—The above acid (0·2 g.) was refluxed with phosphoric oxide (1 g.) in benzene (20 ml.) for 1 hr., then poured on ice, and the organic layer was separated. The aqueous layer, containing charred material, was washed with chloroform, and the combined organic extracts were washed with sodium hydrogen carbonate solution and water and dried (Na_2SO_4). Removal of the solvents left the *ketone*, crystallising from methanol (in a freezing mixture) as pale yellow needles (0·12 g.), m. p. 212—213° (Found: C, 61·6; H, 5·0. $C_{15}H_{14}O_6$ requires C, 62·0; H, 4·9%) undepressed on admixture with tri-*O*-methylbrevifolin, m. p. 213—214°, kindly supplied by Professor Schmidt. The 2 : 4-dinitrophenylhydrazone separated from ethyl acetate as red needles, m. p. and mixed m. p. 294—296° (decomp.). The *p-nitrophenylhydrazone*, prepared in acetic acid, crystallised from anisole as deep red rhombs, m. p. 284—286° (decomp.) (Found: N, 10·3. $C_{21}H_{19}O_7N_5$ requires N, 9·9%).

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84. *The Thermochemistry of Organic Phosphorus Compounds. Part II.* Ester and Anilide Formation from Halides, and Combustion of the Anilides.*

By E. NEALE, L. T. D. WILLIAMS, and (in part) V. T. MOORES.

In continuation of the work reported in Part I * reaction calorimetry has been extended to cover ester formation from tervalent and quinquevalent phosphorus halides and also anilide formation from alkylphosphonic dihalides. Heats of combustion of the anilides have also been determined. The combined data have permitted the compilation of a table of "average bond-energy" terms from which it is possible to make an approximate estimate of heats of formation or reaction of most compounds in the organophosphorus field.

THIS work continues that reported in Part I,* in order to obtain sufficient data to permit the compilation of a table of average bond-energy terms to be used to estimate heats of formation or reaction of organic compounds containing phosphorus. Reaction calorimetry has been extended to include ester formation from tervalent and quinquevalent phosphorus halides and alcohols in the presence of a tertiary base, and also the formation of anilides from alkylphosphonic dihalides. None of the reactions, however, gave direct information on the carbon–phosphorus bond. Considerable difficulty was experienced in the application of usual methods of combustion calorimetry to phosphorus compounds, the majority

* Part I, *J.*, 1955, 2485.

being hygroscopic liquids which gave erratic results suggestive of incomplete burning. An exception was, however, found in the dianilides; they are non-hygroscopic solids, and although the precision achieved was well below that of the most refined modern techniques, results were sufficiently consistent to provide, with those from reaction calorimetry useful data to estimate (1) the heats of formation of the alkylphosphonic dihalides and (2) the average bond-energy term to be assigned to the carbon–phosphorus bond.

Experimental

Preparation of Compounds.—Purification of phosphorus trichloride and preparation and purification of methyl- and ethyl-phosphonic dichlorides were effected as already described.[1] Methyl- and ethyl-phosphonic dianilides were prepared by treating the appropriate alkylphosphonic dichloride with excess of aniline, dissolving the product in benzene, and washing the solution with dilute hydrochloric acid. The anilides were recrystallised first from benzene–chloroform and then aqueous alcohol: *methylphosphonic dianilide* had m. p. 158° (Found: C, 63·2; H, 6·3. $C_{13}H_{15}ON_2P$ requires C, 63·4; H, 6·1%), and *ethylphosphonic dianilide*, m. p. 147° (Found: C, 64·6; H, 6·7. $C_{14}H_{17}ON_2P$ requires C, 64·5; H, 6·6%).

Reaction Calorimetry.—The Dewar-vessel calorimeter and procedure were as in earlier work.[1] Samples were filled into glass ampoules in a glove-box through which dry air or dry nitrogen was passed. Phosphorus trichloride was esterified in *cyclo*hexane (sodium-dried) with dimethylaniline ("AnalaR" dried over KOH) as the tertiary base. These conditions were not satisfactory for esterification of alkylphosphonic halides; dioxan ("AnalaR" sodium-dried) with triethylamine was found to be most suitable. Triethylamine was purified by recrystallisation of the hydrochloride; the purified product was dried by distillation over barium oxide.

Absolute alcohol was dried by distillation after refluxing with magnesium turnings and iodine; *iso*propanol ("AnalaR") was distilled over aluminium *iso*propoxide.

The heat of anilide formation was also measured in *cyclo*hexane in which both the anilides and the aniline hydrochloride produced in the reaction were insoluble, thus minimising the work of measuring heats of solution. Ethylphosphonic dichloride, being a liquid at room temperature, was introduced undiluted, but methylphosphonic dichloride, a solid, gave more consistent results when added as a concentrated solution in benzene. Aniline was distilled over zinc dust and dried (KOH).

Heats of solution were measured in the apparatus used for the main reactions. It was also necessary to determine the heats of formation of the base hydrochlorides; in the case of aniline and dimethylaniline the heats of hydrolysis of the salts in aqueous sodium hydroxide were measured. Erratic results were obtained by this technique for triethylamine hydrochloride, but the necessary results were satisfactorily obtained by breaking an ampoule containing a weighed amount of standard hydrochloric acid into an aqueous solution of triethylamine.

As an analytical check on reactions with aniline and esterification in the presence of dimethylaniline, the base hydrochlorides were filtered off and titrated against sodium hydroxide with phenolphthalein as indicator. In reactions involving triethylamine the hydrochloride was recovered and estimated by titration of chloride ion. All reactions were carried out at 22—23°.

Combustion Calorimetry.—The calorimeter and jacket which were made of chromium-plated copper were similar to those described by Dickinson.[2] The stainless-steel bomb (300 ml. capacity) was of the standard B.T.L. Type (L.F.A. 6330). Temperature was measured by a mercury-in-glass thermometer of range 21—27° graduated to 0·01° and calibrated to 0·001°. All combustions were carried out in 30 atm. of oxygen, with the bomb containing 10 ml. of water. The water equivalent of the apparatus was assessed by repeated combustion of benzoic acid obtained from the Bureau of Analysed Samples Ltd.; results were reproducible to within ±0·1%.

Considerable difficulty was encountered in the choice of a crucible. Silica was first used but there was evidence of attack by the phosphoric acid produced; nickel, fused alumina, and fused zirconia were also tried and rejected. Platinum was finally adopted; it appeared to be unattacked chemically although there was evidence of physical change (development of cracks) after repeated use. The samples were fused in the crucible before being weighed, the amount taken being such as to give ΔT within 0·1° of that in the benzoic acid calibration. Combustion

[1] Neale and Williams, *J.*, 1954, 2156; 1955, 2485.
[2] Dickinson, *Nat. Bur. Stand. Bull.*, 1915, **17**, 189.

was started with the calorimeter at 22·00°; the final temperature was approximately that of the thermostat (25°). Washburn corrections were not applied.

In the preliminary experiments the combustion products were analysed for ortho-, pyro-, and meta-phosphoric acid; results showed that 93—96% was present as orthophosphoric acid. As the error involved in treating the whole as the last acid would not exceed 0·3—0·4 kcal. under the worst conditions it was decided to determine only total phosphoric acid; Wilson's quinoline–phosphomolybdate method [3] was used. Nitric acid in the bomb was also determined by the phenoldisulphonic acid method.

Latent heats of vaporisation were estimated from vapour-pressure data except where published information was available. Subsidiary thermochemical data used in deriving heats of formation and average bond-energy terms were taken from the National Bureau of Standards Circular 500 (Feb. 1952).

Results.—(a) *Esterification of phosphorus trichloride with alcohols in the presence of dimethylaniline* (*solvent,* cyclo*hexane*):

$$PCl_3\ (liq.) + 3ROH\ (soln.) + 3Ph{\cdot}NMe_2\ (soln.) \longrightarrow P(OR)_3\ (soln.) + 3Ph{\cdot}NMe_2{,}HCl\ (solid) \quad . \quad (1)$$

Approximately 4 moles of alcohol and 4 moles of base were taken for each mole of phosphorus trichloride. Results were as follows:

(i) Ethyl alcohol			(ii) *iso*Propyl alcohol		
Wt. of PCl_3 (g.)	Moles of solvent per mole of PCl_3	$\Delta H_{obs.}$ (kcal.)	Wt. of PCl_3 (g.)	Moles of solvent per mole of PCl_3	$\Delta H_{obs.}$ (kcal.)
1·0281	610	−89·6	0·8610	730	−90·7
0·9302	680	−90·5	0·7701	820	−90·4
0·5705	1100	−91·0	0·6315	1000	−91·2
	Mean	−90·4		Mean	−90·8

Recovery of dimethylaniline hydrochloride as determined by titration with standard alkali varied between 98 and 99% of theoretical; no correction was applied to $\Delta H_{obs.}$ on this account.

For the reaction of dimethylaniline hydrochloride with aqueous sodium hydroxide (0·2N):

$$Ph{\cdot}NMe_2{,}HCl\ (solid) + NaOH\ (aq.) \longrightarrow Ph{\cdot}NMe_2\ (liq.) + NaCl\ (aq.) + H_2O\ (liq.) \quad . \quad (2)$$

$\Delta H_{obs.} = -5{\cdot}8$ kcal./mole, whence $\Delta H_f°(Ph{\cdot}NMe_2{,}HCl) = \Delta H_f°(Ph{\cdot}NMe_2) - 47{\cdot}6$ kcal. Heats of solution in *cyclo*hexane (in kcal./mole) were as folows: Dimethylaniline, +1·7; ethyl alcohol, +4·7; *iso*propyl alcohol, +4·2; triethyl phosphite, +1·5; tri*iso*propyl phosphite, +0·8. Substituting the above data in equation (1), we get: $\Delta H_f°[P(OEt)_3]$ (liq.) = −203·5 kcal./mole, and $\Delta H_f°[P(OPr^i)_3]$ (liq.) = −235·0 kcal./mole.

With allowance for both calorimetric and chemical errors these values are probably reliable to within ±2·0 kcal.

(b) *Esterification of alkylphosphonic dichlorides with alcohols in the presence of triethylamine* (*solvent, dioxan*):

$$R{\cdot}POCl_2 + 2R'OH\ (soln.) + 2Et_3N\ (soln.) \longrightarrow R{\cdot}PO(OR')_2\ (soln.) + 2Et_3N{,}HCl\ (solid) \quad . \quad (3)$$

3—4 Moles of alcohol and base were used for each mole of $R{\cdot}POCl_2$. The results are given below.

(i) R = Me, R′ = Et			(ii) R = Et, R′ = Pr^i		
Wt. of $R{\cdot}POCl_2$ (g.)	Moles of solvent per mole of $R{\cdot}POCl_2$	$\Delta H_{obs.}$ (kcal.)	Wt. of $R{\cdot}POCl_2$ (g.)	Moles of solvent per mole of $R{\cdot}POCl_2$	$\Delta H_{obs.}$ (kcal.)
0·8760	870	−89·2	0·8167	1000	−93·7
0·9851	770	−89·4	0·8596	975	−93·5
0·6322	1200	−90·1	0·6885	1200	−94·0
0·7480	1000	−88·5	0·7405	1100	−92·8
	Mean	−89·3		Mean	−93·5

Recovery of triethylamine hydrochloride as determined by estimation of chloride was 97·8—98·6% of theoretical; values of $\Delta H_{obs.}$ were not corrected for this. The reaction of triethylamine with aqueous hydrochloric acid:

$$Et_3N\ (aq.) + HCl\ (aq.) \longrightarrow Et_3N{,}HCl\ (aq.) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

whence $\Delta H_f°(Et_3N{,}HCl) = \Delta H_f°(Et_3N) - 60{\cdot}3$ kcal.

[3] Wilson, *Analyst*, 1951, **76**, 65.

Heats of solution (kcal./mole) in dioxan were as follows: triethylamine, +1·0; ethyl alcohol, +1·5; *iso*propyl alcohol, +1·6; diethyl methylphosphonate, +0·6; di*iso*propyl ethylphosphonate, +0·4. Substituting the above data in equation (3) we get: ΔH_f°[Me·POCl$_2$] (cryst.) − ΔH_f°[Me·PO(OEt)$_2$] (liq.) = +97·1 kcal., and ΔH_f° [Et·POCl$_2$] (liq.) − ΔH_f° [EtPO(OPr^i)$_2$] (liq.) = +121·1 kcal. These values are probably reliable to within ±2·0 kcal.

(c) *Reaction between alkylphosphonic dichlorides and aniline (solvent,* cyclo*hexane)*:

$$R{\cdot}POCl_2 + 4Ph{\cdot}NH_2\ (soln.) \longrightarrow R{\cdot}PO(NHPh)_2\ (solid) + 2Ph{\cdot}NH_2,HCl\ (solid). \quad . \quad (5)$$

The calorimeter filling was approximately 0·5M with respect to aniline. The results are given below.

(i) R = Me			(ii) R = Et		
Wt. of Me·POCl$_2$ (g.)	Moles of solvent per mole of Me·POCl$_2$	$\Delta H_{obs.}$ (kcal.)	Wt. of Et·POCl$_2$ (g.)	Moles of solvent per mole of Et·POCl$_2$	$\Delta H_{obs.}$ (kcal.)
0·7676	760	−71·6	1·0917	590	−72·5
0·6204	940	−71·9	0·6697	970	−73·6
0·5849	1000	−71·9	0·5116	1260	−72·4
0·6227	940	−71·8	0·7196	900	−72·1
	Mean	−71·8		Mean	−72·7

Extraction of the precipitates with water and titration with sodium hydroxide (phenolphthalein) gave 1·99—2·01 moles of aniline hydrochloride per mole of R·POCl$_2$.

For the reaction of aniline hydrochloride with aqueous sodium hydroxide (0·2N):

$$Ph{\cdot}NH_2,HCl\ (solid) + NaOH\ (aq.) \longrightarrow Ph{\cdot}NH_2\ (liq.) + NaCl\ (aq.) + H_2O\ (liq.) \quad . \quad (6)$$

ΔH, obs. = −3·2 kcal./mole, whence ΔH_f°(Ph·NH$_2$,HCl) = −42·9 kcal./mole. The heat of solution of Me·POCl$_2$ in benzene was +3·6; and that of aniline in *cyclo*hexane, +3·8 kcal./mole. The heat of mixing of benzene and *cyclo*hexane is shown by Baud [4] to be negligible for the present purpose.

Applying the above data to equation (5), we have: ΔH_f°(Me·POCl$_2$) (cryst.) − ΔH_f°[Me·PO(NHPh)$_2$] (cryst.) = −62·2 kcal., and ΔH_f°(Et·POCl$_2$) (liq.) − ΔH_f°[Et·PO(NHPh)$_2$] (cryst.) = −57·7 kcal. ± 1·0 kcal. in each case.

(d) *Combustion of methylphosphonic dianilide*: The heat of combustion (mean of six measurements) was −1857 kcal./mole (standard deviation ±3·0 kcal.). 99·2—100·8% of the theoretical H_3PO_4 was recovered, and 12·2—16·5% (mean 14%) of the available nitrogen was found to be present as HNO_3.

The approximate concentration of aqueous nitric acid in the bomb was 0·14M. The necessary correction for the formation of HNO_3,aq. from N_2 (g.), O_2 (g.), and H_2O (liq.) being +13·8 kcal./mole of HNO_3, the corrected heat of combustion is ΔU_B = −1857 + (2 × 0·14 × 13·8) = −1853 kcal./mole.

The complete reaction may now be expressed as:

$$C_{13}H_{15}ON_2P\ (cryst.) + 17\tfrac{1}{2}O_2\ (g.) \longrightarrow 13CO_2\ (g.) + N_2\ (g.) + 6H_2O\ (liq.) + H_3PO_4\ (aq.) \quad . \quad (7)$$

As the reaction results in a decrease of 3·5 gaseous molecules we have:

$$\Delta U_B = \Delta H + 3{\cdot}5RT \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

Therefore ΔH = −1855 kcal./mole.

The correct dilution to be allowed for the phosphoric acid is complicated by the fact that 85% was in the 10 ml. of water in the bomb (concentration *ca.* 0·5M), the remainder being in about 0·5 ml. of liquid in the crucible (concentration *ca.* 2M). We have therefore taken an average value of ΔH_f°(H_3PO_4) (aq.) = −309·0 kcal./mole. Substituting this value and those for CO_2 (g.) and H_2O (liq.) given in N.B.S. Circular 500 (1952), in equation (7), we obtain:

$$\Delta H_f^\circ[Me{\cdot}PO(NHPh)_2]\ (cryst.) = -86{\cdot}6\ kcal./mole$$

which when applied to the result on the formation of anilide from dihalide [(c) above] gives

$$\Delta H_f^\circ[Me{\cdot}POCl_2]\ (cryst.) = -148{\cdot}8\ kcal./mole.$$

(e) *Combustion of ethylphosphonic dianilide.* The heat of combustion (mean of seven measurements) was −2016 kcal./mole (standard deviation ±1·5 kcal.).

[4] Baud, *Bull. Soc. chim. France*, 1915, **17**, 329.

99·5—101·2% of the theoretical H_3PO_4 was recovered.

13·0—15·4% (mean 14%) of the available nitrogen was found to be present as HNO_3. The heat of combustion, corrected for nitric acid formation, is therefore $\Delta U_R = -2012$ kcal./mole.

$$C_{14}H_{17}ON_2P\ (cryst.) + 19O_2\ (g.) \longrightarrow 14CO_2\ (g.) + N_2\ (g.) + 7H_2O\ (liq.) + H_3PO_4\ (aq.) \quad (9)$$

Hence
$$\Delta U_R = \Delta H + 4{\cdot}0RT \quad (10)$$

$\Delta H = -2014{\cdot}3$ kcal./mole and ΔH_f°[Et·PO(NHPh)$_2$] (cryst.) $= -89{\cdot}6$ kcal./mole.

This value, substituted in the result on the formation of anilide from dihalide, gives: ΔH_f°(Et·POCl$_2$) (liq.) $= -147{\cdot}3$ kcal./mole.

Discussion

The procedure followed in deriving bond-energy terms from the experimental data is the same as that used earlier.[1b] Some explanation is, however, necessary regarding the values assumed for the heats of formation of alkyl and ester groups. In so far as the identity of a group is not changed in a reaction the value assumed for its heat of formation is to some extent immaterial, but a consistent procedure is obviously desirable. Charnley, Mortimer, and Skinner [5] used values for the radicals R· and RO· when calculating the more fundamental parameter—the " bond-dissociation energy "—but the number of radicals for which such data are available is very limited. We have followed the simple if somewhat empirical method of estimating values for alkyl and ester groups from the parent hydrocarbon or alcohol respectively:

$$Q_f(a)R = Q_f(a)RH - \bar{D}(C{-}H)$$
$$Q_f(a)OR = Q_f(a)ROH - \bar{D}(O{-}H)$$

$\bar{D}$(C–H) and $\bar{D}$(O–H) being derived from methane and water.

On this basis the average bond-energy term for the P–OR link in tervalent phosphorus esters can be derived directly from the heats of formation of the tertiary esters given above:

$$\bar{D}(P{-}OR) = \tfrac{1}{3}Qf(a)[(RO)_3P] - Q_f(a)OR$$

	ΔH_f° (liq.) (kcal.)	Heat of vapn. (kcal.)	$\bar{D}$(P–OR) (kcal.)
$(EtO)_3P$	−203·5	10·0	91·9
$(Pr^iO)_3P$	−235·0	11·6	92·3

Similarly the P–OR link in quinquevalent phosphorus compounds can be evaluated from the results on the esterification of the alkylphosphonic dihalides [(b) above]:

$$\bar{D}(P{-}OR) = \tfrac{1}{2}\{Q_f(a)[R'{\cdot}PO(OR)_2] - Q_f(a)[R'{\cdot}POCl_2]\} - Q_f(a)OR + \bar{D}(P{-}Cl)$$

	ΔH_f° (kcal.)	Heat of vapn. (or sublimn.) (kcal.)	$\bar{D}$(P–OR) (kcal.)
Me·$POCl_2$ (cryst.)		14·9	
Me·$PO(OEt)_2$ (liq.)	+ 97·1	13·5	102·9
Et·$POCl_2$ (liq.)		10·2	
Et·$PO(OPr^i)_2$ (liq.)	+121·1	14·5	102·4

The bond energy term for the C–P bond in quinquevalent phosphorus compounds can be estimated directly from the values given in (d) and (e) above for the heats of formation of the alkylphosphonic dihalides; the value assumed for $\bar{D}$(P=O) is that used in Part I,[1b] namely, 115·0 kcal.:

$$\bar{D}(C{-}P) = Q_f(a)(R{\cdot}POCl_2) - Q_f(a)R - \bar{D}(P{=}O) - 2\bar{D}(P{-}Cl)$$

	ΔH_f° (kcal.)	Heat of vapn. (or sublimn.) (kcal.)	$\bar{D}$(C–P) (kcal.)
Me·$POCl_2$ (cryst.)	−148·8	14·9	80·0
Et·$POCl_2$ (liq.)	−147·3	10·2	80·9

The apparent increase in the bond energy of the P–OR bond in quinquevalent, as compared with tervalent, esters is not necessarily real, as the thermochemical measurements are composite and embody other changes in energy distribution within the molecule. The difference is however quite consistent with the evidence obtained here (see Part I) and at

[5] Charnley, Mortimer, and Skinner, *J.*, 1953, 1181.

Manchester University [6] that the bond-dissociation energy of the phosphoryl bond appears to be considerably greater in phosphate esters than in phosphonyl halides. This may be due to resonance between the oxygen in P=O and that in P–OR increasing the overall stability of the molecule and thus giving rise to an apparent increase in bond energy in the circumstances of the present measurements.

The average bond energy terms (in kcal.) derived in this investigation are summarised below :

Bond	Tervalent P	Quinquevalent P (containing P=O bond)	Bond	Tervalent P	Quinquevalent P (containing P=O bond)
P–O	—	115·0	P–OH	—	104·5
P–F	117	120·0	P–OR	92·1	102·5
P–Cl	76·3	80·0	P–OP	—	96·0
P–Br	61·7	65·0	P–C	—	80·5
P–H	76·3	78·0			

The reliability of these estimates for predicting heats of formation or reaction can only be tested as other independent thermochemical data become available. A test of their internal consistency is, however, provided by comparing ΔH_f° values calculated from the above table with those obtained directly in the course of experiments :

	$-\Delta H_f^\circ$ (kcal.) : calc.	obs.		$-\Delta H_f^\circ$ (kcal.) : calc.	obs.
$Me{\cdot}POCl_2$ (solid)	148·5	148·8	$Me{\cdot}PO(OEt)_2$ (liquid)	245·5	245·9
$Et{\cdot}POCl_2$ (liquid)	146·1	147·3	$Et{\cdot}PO(OPr^i)_2$ (liquid)	268·2	268·4
$Me{\cdot}PO(OH)_2$ (solid)	250·7	252·6	$P(OEt)_3$ (liquid)	204·2	203·5
$Et{\cdot}PO(OH)_2$ (solid)	253·6	253·5	$P(OPr^i)_3$ (liquid)	234·3	235·0

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Porton.

[*Received, August 15th*, 1955.]

[6] Skinner, personal communication.

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85. *Peroxides as Initiators of Polymerization of Methyl Methacrylate.*

By (the late) N. G. Saha, U. S. Nandi, and Santi R. Palit.

The polymerisation of methyl methacrylate, both homogeneous and in benzene, toluene, and ethyl acetate, has been initiated with nine diacyl peroxides at 60°. The kinetic order of the reaction with respect to the initiators and the monomer is found to be $\frac{1}{2}$ and $\frac{3}{2}$, respectively, in all cases. The value of δ (Table 1) for methyl methacrylate at 60° has been determined at different monomer concentrations initiated by each peroxide and a mean value of 7·60 is obtained.

The initiation constants of all the diacyl peroxides have been determined by two independent methods (rate, and degree of polymerisation) which give similar results, the constants being increased by electron-releasing groups in the benzene ring.

The chain-transfer coefficients for monomer (C_M), initiator (C_I), and solvents (C_S) have also been determined by various methods. The value of C_M is 1×10^{-5}; an attempt has been made to correlate values of C_I with the structure of the peroxides. The chain-transfer coefficients for solvents could be determined very accurately (in agreement with recorded values) in the presence of any type of peroxide from the known values of C_M and C_I with the help of the general equation for degree of polymerisation.

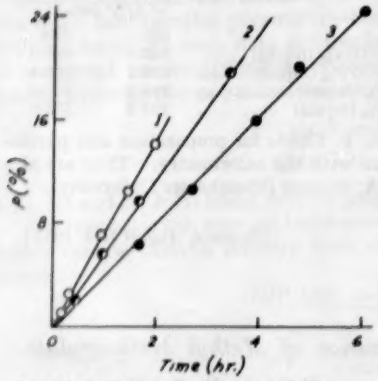
We have polymerised methyl methacrylate with diacyl peroxides both in bulk and in solution and have determined various kinetic constants, especially the chain-transfer coefficients for monomer (C_M), initiators (C_I), and solvents (C_S). The influence of substituents in the benzene ring of the peroxide on initiation and on catalyst-transfer reaction

has also been studied, and the results are compared with those reported by Cooper [1] for the polymerization of styrene.

Yield Curves.—Methyl methacrylate was polymerized with varying concentrations of catalyst (0·0006—0·14 mole/l.) in bulk and in solutions in ethyl acetate and toluene at 60°. Some typical yield curves are represented in Fig. 1. They are good straight lines passing through the origin, thus showing that there is practically no inhibition period under any conditions, so in subsequent experiments the rate of polymerization was calculated from the yield of a single tube.

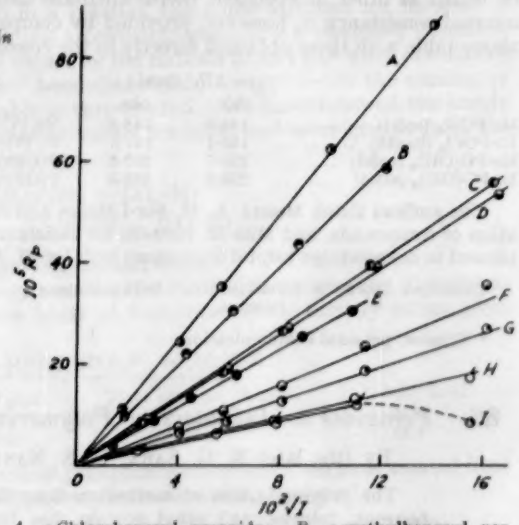
Dependence of the Rate of Polymerization, R_p, on Catalyst Concentration.—The relation between the initiator concentration and the rate of polymerization was studied at different monomer concentrations with nine diacyl peroxides at 60°. The results are shown in Tables 1 and 2 and Fig. 2. Thomas and Pellon [2] have shown recently that in the bulk

FIG. 1. *Determination of inhibition period in catalyzed polymerization at 60°.*



1, *o*-Methylbenzoyl peroxide in bulk.
2, *o*-Methylbenzoyl peroxide in ethyl acetate (4·645M).
3, *o*-Chlorobenzoyl peroxide in toluene.

FIG. 2. *Determination of the order of reaction with respect to initiator concentration in bulk.*



A, *o*-Chlorobenzoyl peroxide; *B*, *o*-methylbenzoyl peroxide; *C*, anisoyl peroxide; *D*, cinnamoyl peroxide; *E*, palmitoyl peroxide; *F*, *G*, *p*-, *m*-chlorobenzoyl peroxide; *H*, *I*, *m*-, *p*-nitrobenzoyl peroxide.

polymerization of acrylonitrile with benzoyl peroxide R_p is proportional to $I^{0.75}$ but in all cases studied by us we find it to be proportional to the square root of the catalyst concentration, in agreement with the usual equation [3]

$$R_p = (k_p/k_t^{\frac{1}{2}})k_i^{\frac{1}{2}}M^1I^{\frac{1}{2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where I and M are the initiator and monomer concentrations respectively, and k_p, k_i, and k_t are the rate constants for propagation, initiation, and termination processes respectively. The straight lines pass through the origin, again showing that there is no inhibition period and very little superimposed thermal reaction, and termination is probably by a bimolecular free-radical interaction. Nitrobenzoyl peroxides, especially the *para*-substituted one, show abnormal behaviour, the rate decreasing with increasing catalyst concentration. This is attributed to the inhibiting effect of nitro-compounds on polymerization, which is confirmed by the failure to follow the square-root relation ($I^{\frac{1}{2}}$).

[1] Cooper, *J.*, 1951, 3106; 1952, 2408.
[2] Thomas and Pellon, *J. Polymer Sci.*, 1954, **13**, 329.
[3] Bawn, "Chemistry of High Polymers," Interscience Publ. Inc., p. 67.

TABLE 1. *Polymerization of methyl methacrylate in bulk (9·29 moles/l.) in presence of catalysts at 60°.*

$10^3\,I/M$	10^3R_p *	$10^3/\overline{P}$	
Catalyst : *o*-Chlorobenzoyl peroxide.			
2·08	86·40	62·13	$10^6R_p^2/I = 36·73$
1·04	62·20	42·76	$10^6k_t = 2·64, 2·84$ †
0·35	35·50	25·17	$\delta = 7·55$
0·17	24·40	17·80	$C_I = 0·02$
0·03	11·20	8·16	$10^5C_M = 0·90$
Catalyst : *p*-Methoxybenzoyl peroxide.			
2·84	55·62	42·76	$10^6R_p^2/I = 12·26$
1·42	39·45	24·98	$10^6k_t = 0·88, 0·62$
0·71	26·41	18·20	$\delta = 7·22$
0·35	18·32	12·57	$C_I = 0·04$
0·07	8·94	7·01	$10^5C_M = 1·00$
Catalyst : palmitoyl peroxide.			
1·26	30·61	25·37	$10^6R_p^2/I = 8·40$
0·84	25·31	20·65	$10^6k_t = 0·60, 0·61$
0·42	18·16	16·14	$\delta = 8·25$
0·21	13·49	11·03	$C_I = \sim 0$
0·10	9·04	8·53	$10^5C_M = 0·97$
0·02	4·17	4·14	
Catalyst : *m*-Chlorobenzoyl peroxide.			
2·77	27·20	14·54	$10^6R_p^2/I = 2·25$
1·38	18·51	11·64	$10^6k_t = 0·16$, —
0·69	12·80	8·31	$\delta = 8·12$
0·34	8·91	6·44	$C_I = 0·003$
0·17	6·12	5·18	$10^5C_M = 1·00$
Catalyst : *p*-Nitrobenzoyl peroxide.			
2·56	8·80	48·98	$10^6R_p^2/I = 1·21$
1·28	12·56	27·98	$10^6k_t = 0·09, 0·09$
0·64	8·75	15·51	$\delta = 7·66$
0·32	6·41	9·37	$C_I = 0·144$
0·06	2·69	4·32	$10^5C_M = 1·05$

$10^3\,I/M$	10^3R_p *	$10^3/\overline{P}$	
Catalyst : *o*-Methylbenzoyl peroxide.			
1·59	58·05	46·66	$10^6R_p^2/I = 25·0$
0·80	43·58	31·39	$10^6k_t = 1·79, 1·73$
0·40	30·86	21·04	$\delta = 7·22$
0·20	22·40	16·50	$C_I = 0·05$
0·04	9·77	7·01	$10^5C_M = 1·10$
Catalyst : Cinnamoyl peroxide.			
2·93	53·29	42·76	$10^6R_p^2/I = 10·56$
1·46	39·50	31·39	$10^6k_t = 0·76, 0·79$
0·73	27·45	22·65	$\delta = 7·95$
0·36	19·10	15·50	$C_I = 0·009$
0·07	9·43	9·46	$10^5C_M = 1·01$
Catalyst : *p*-Chlorobenzoyl peroxide.			
2·77	35·32	13·77	$10^6R_p^2/I = 4·00$
1·38	24·13	11·32	$10^6k_t = 0·29$ —
0·69	15·75	8·42	$\delta = 7·80$
0·34	10·84	6·49	$C_I = 0·009$
0·17	6·91	5·56	$10^5C_M = 1·03$
Catalyst : *m*-Nitrobenzoyl peroxide.			
2·56	17·86	17·80	$10^6R_p^2/I = 1·40$
1·28	13·34	11·45	$10^6k_t = 0·10, 0·11$
0·64	9·00	7·48	$\delta = 7·55$
0·32	6·72	5·69	$C_I = 0·012$
0·06	2·89	3·51	$10^5C_M = 1·20$

* R_p is given in mole $l.^{-1}$ $sec.^{-1}$.

† In all these entries for 10^6k_t the first number is that determined by the R_p method, and the second that by the degree of polymerization method.

TABLE 2. *Polymerization of methyl methacrylate in solution in presence of catalyst at 60°.*

Catalyst : *o*-Methylbenzoyl peroxide. Solvent : Toluene. 10^5C_s (uncatalyzed) = 2·00.

$10^3\sqrt{I/M}$	S/M	10^3R_p *	$10^3/\overline{P}$	10^5C_s † (1)	(2)
19·95	1·005	10·70	40·83		
13·91	,,	7·64	27·98	1·73	2·35
6·30	,,	3·10	14·26		
19·95	2·345	4·90	44·77		
13·91	,,	3·50	31·20	1·70	1·80
6·30	,,	1·50	16·88		
19·95	4·020	2·10	49·00		
13·91	,,	1·50	36·66	1·90	2·20
6·30	,,	0·60	20·84		

Catalyst : Palmitoyl peroxide. Solvent : Ethyl acetate. 10^5C_s (uncatalysed) = 1·30.

29·04	1·112	5·42	27·77		
20·05	,,	4·38	23·50		
14·50	,,	3·25	16·38	1·32	1·36
10·27	,,	2·28	11·84		
4·56	,,	,,	6·15		

Catalyst : Palmitoyl peroxide. Solvent : Ethyl acetate. 10^5C_s (uncatalyzed) = 1·30.

$10^3\sqrt{I/M}$	S/M	10^3R_p *	$10^3/\overline{P}$	10^5C_s † (1)	(2)
29·04	2·594	3·12	31·38		
20·05	,,	2·10	26·27		
14·50	,,	1·90	19·63	1·00	1·20
10·27	,,	0·88	14·43		
4·56	,,	—	7·21		
29·04	4·448	0·89	39·72		
20·05	,,	0·70	30·81		
14·50	,,	0·31	21·23	1·00	1·33
10·27	,,	0·09	16·62		
4·56	,,	—	7·69		
29·04	10·008	0·30	53·95		
20·05	,,	0·13	40·36	1·00	1·41
14·50	,,	—	29·58		
10·27	,,	—	17·94		

* R_p in mole $l.^{-1}$ $sec.^{-1}$.

† From intercept of curve of $(1/\overline{P} - C_I I/M)$ against (1) $\sqrt{I/M}$ and (2) R_p.

Dependence of R_p on M.—Since the kinetic order of $\frac{3}{2}$ with respect to monomer concentration (eqn. 1) is not always followed, we have determined the kinetic order with respect to monomer with all the catalysts at various concentrations in both the solvents. It can be easily shown that the theoretical slope of the plot of log R_p against log M should be $(n + \frac{1}{2})$ at constant values of I/M, where n is the actual kinetic order. From Fig. 3, with the data given in Tables 1 and 2, it is seen that in all cases studied the order is $\frac{3}{2}$ with respect

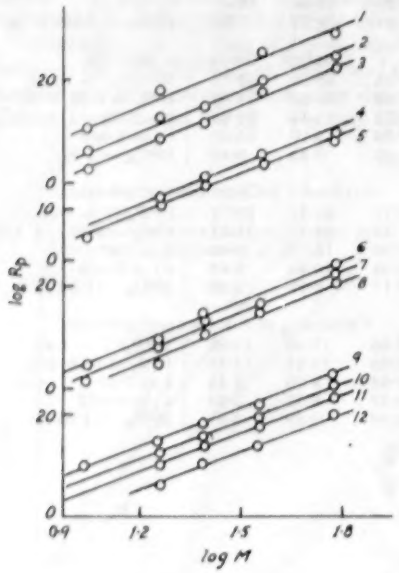


FIG. 3. *Determination of the order of reaction with respect to monomer concentration in ethyl acetate.*
1, Anisoyl peroxide.
2, 3, Cinnamoyl peroxide.
4, 5, *o*-Methylbenzoyl peroxide.
6, 7, 8, Palmitoyl peroxide.
9—12, *o*-Chlorobenzoyl peroxide.

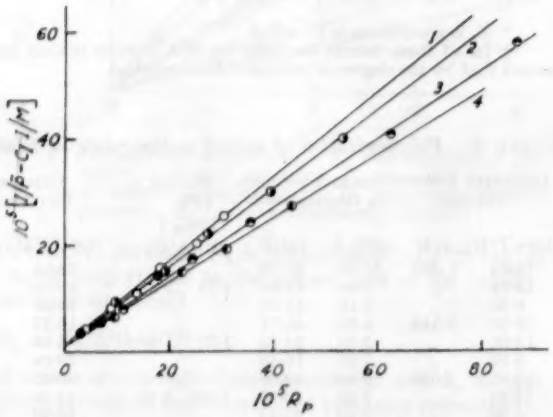


FIG. 4. *Determination of δ for methyl methacrylate at 60°.*
1, Palmitoyl peroxide.
2, Cinnamoyl peroxide.
3, *o*-Chlorobenzoyl peroxide.
4, *o*-Methylbenzoyl peroxide.

to monomer concentration, so the bimolecular initiation mechanism which we have assumed in the methyl methacrylate-catalysed polymerization [4] is followed. Andréconix and Smets [5] have reported the reaction to be of first order with respect to monomer concentration in the polymerization of methyl methacrylate in benzene solution and of somewhat higher order in *tert.*-butylbenzene. They attributed the difference to the influence of the solvent molecules on the induced rate of decomposition of the peroxide, as well as to a

[4] Basu, Sen, and Palit, *Proc. Roy. Soc.*, 1950, *A*, **202**, 485; 1952, *A*, **214**, 247.
[5] Andréconix and Smets, *J. Polymer Sci.*, 1953, **10**, 525.

" cage effect." It is, however, well known that solvent plays an important part in the decomposition of peroxides, which in turn affects the initiation reaction, so the above change may be due to a change in the initiation reaction.

The Value of δ for Methyl Methacrylate.—The ratio of the square root of the termination constant to the propagation constant, $k_t^{\frac{1}{2}}/k_p = \delta$, is of fundamental importance in the determination of kinetic constants in polymerization. Reported values vary,[6] so we have calculated its value from our results, with the help of the general equation for the degree of polymerization :[6d,7]

$$1/\overline{P} = C_M + C_S(S/M) + C_I(I/M) + R_p\delta^2/M^2 \quad . \quad . \quad . \quad . \quad . \quad (2)$$

According to this equation the plot of $[(1/\overline{P} - C_I(I/M)]$ against R_p at constant monomer concentration should give a straight line from the slope of which the value of δ can be calculated. The value of C_I was determined for different peroxides by an independent method (see Table 1). For bulk polymerization the above plot, with the data in Table 1, gives straight lines shown in Fig. 4. From the slopes of these straight lines, the value of δ obtained (Table 1) seems to vary slightly with the peroxide used. For palmitoyl

TABLE 3. *Polymerization of methyl methacrylate in toluene in presence of catalyst at 60°.*

$10^3I/M$	S/M	10^5R_p *	$10^5/\overline{P}$	10^5C_S † (1)	10^5C_S † (2)	$10^3I/M$	S/M	10^5R_p *	$10^5/\overline{P}$	10^5C_S † (1)	10^5C_S † (2)
Catalyst : *p*-Methoxybenzoyl peroxide.											
26·66	1·005	11·22	33·57		2·10	26·66	4·020	1·89	44·45	4·00	1·90
,,	2·345	—	37·56	4·00	—	,,	9·045	0·37	64·18	4·00	—
Catalyst : Cinnamoyl peroxide											
27·04	1·005	10·95	33·52		2·20	19·13	1·005	6·40	26·54		
,,	2·345	3·12	40·36	5·00	—	,,	2·345	1·52	30·00	2·50	—
,,	4·020	1·86	46·66		3·00	,,	4·020	0·73	34·98		
,,	9·045	0·40	73·01		—	,,	9·045	0·18	47·00		
Catalyst : *m*-Nitrobenzoyl peroxide.											
25·39	1·005	—	9·18			12·75	1·005	—	7·10		
,,	2·345	—	12·54	2·70	—	,,	2·345	—	10·58	2·00	—
,,	4·020	—	18·20			,,	4·020	—	13·45		
,,	9·045	—	32·00								

* In mole $l.^{-1}$ $sec.^{-1}$.

† C_S obtained from (1) slope of curve of $1/\overline{P}$ against S/M; (2) equation (4). 10^5C_S (uncatalyzed) = 2·00 throughout.

TABLE 4. *Values of initiation constant (k_i) and δ at different monomer concentrations.*

Monomer concn. (mole/l.)	10^6k_i : *o*-Methylbenzoyl peroxide in toluene	10^6k_i : Palmitoyl peroxide in ethyl acetate	δ
9·290	1·79	0·61	7·22
4·645	5·54	1·31	8·30
2·790	6·20	1·66	7·67
1·858	6·92	2·45	7·68
0·929	—	3·86	—

peroxide, for which the value of C_I is zero, δ, calculated directly from the slope of the plot of $1/P$ against R_p, is 8·25, in good agreement with the values of 8·33 and 8·43 reported by Matheson *et al.*[6c] and Nandi and Palit [6f] respectively. Moreover, it is noteworthy (Table 4) that variation in the monomer concentration or in the nature of the solvent has no marked effect on its value. However, in order that the kinetic constants for the different initiators

[6] (*a*) Bonsal, Valentine, and Melville, *Trans. Faraday Soc.*, 1952, **48**, 765; (*b*) Bamford and Dewar, *Discuss. Faraday Soc.*, 1947, **2**, 310; (*c*) Matheson, Auer, Bevilacqua, and Hart, *J. Amer. Chem. Soc.*, 1949, **71**, 497; (*d*) Baysal and Tobolsky, *J. Polymer Sci.*, 1952, **8**, 529; (*e*) Melville and Burnett, *ibid.*, 1954, **13**, 417; (*f*) Nandi and Palit, *ibid.*, 1955, **17**, 65.

[7] Palit, Nandi, and Saha, *ibid.*, 1954, **14**, 295.

used may be compared with each other the mean value of 7·60 for δ has been used in the present study.

Determination of Initiation Constant (k_i).—The rates of initiation were determined by two different independent methods. The results are summarized in Table 1.

Overall rate (R_p) *method.* In this process, we have determined the value of k_i from the values of R_p with the help of equation (1), in which $k_p/k_t^{\frac{1}{2}}$ has been replaced by δ:

$$k_i = \delta^2 R_p^2/M^2 I \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The value of R_p^2/I, which is different for different peroxides, has been taken from Table 1.

Degree of polymerization method. The initiation constants of both bulk and solution polymerization have also been determined from the general equation (2) for the average degree of polymerization. Equation (2) can be transformed into the form:

$$\left\{\frac{1}{\overline{P}} - C_I\frac{I}{M}\right\} = C_M + C_S\frac{S}{M} + \frac{k_i^{\frac{1}{2}}}{k_p} \cdot k_i^{\frac{1}{2}}\left\{\frac{I}{M}\right\}^{\frac{1}{2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

According to this equation the plot of $[1/\overline{P} - C_I(I/M)]$ against $(I/M)^{\frac{1}{2}}$ at constant monomer concentration gives a straight line (Fig. 5) from the slope of which k_i has been calculated. The values of C_I for different peroxides have been taken from Table 1, and from this Table it is evident that the agreement between the values of k_i, determined by these two methods, is satisfactory within our experimental accuracy. Our values of k_i are comparable with those reported by Cooper,[1] and our results (Table 5) also indicate that the electron-releasing

TABLE 5. *Comparison of initiation and transfer constants of styrene with those of methyl methacrylate.*

Peroxide	Styrene * at 70° 10^6k_i	C_I	Methyl methacrylate at 60° 10^6k_i	C_I	Peroxide	Styrene * at 70° 10^6k_i	C_I	Methyl methacrylate at 60° 10^6k_i	C_I
o-Chlorobenzoyl ...	28·20	1·91	2·64	0·019	*p*-Chlorobenzoyl ...	5·40	0·22	0·29	0·009
o-Methylbenzoyl ...	27·80	0·18	1·79	0·046	*m*-Chlorobenzoyl ...	3·60	0·35	0·16	0·003
p-Methoxybenzoyl	18·50	0·07	0·88	0·037	*m*-Nitrobenzoyl ...	0·70	6·20	0·10	0·012
Cinnamoyl	16·20	—	0·76	0·009	*p*-Nitrobenzoyl ...	0·20	7·40	0·09	0·144
Palmitoyl	15·60	—	0·60	~0					

* Cooper's values (*J.*, 1951, 3106; 1952, 2408).

groups in the *meta*- and the *para*-position in dibenzoyl peroxides increase the rate of initiation in methyl methacrylate also. *o*-Chlorobenzoyl peroxide has a higher value for k_i than those of its *meta*- and *para*-isomers. The order of peroxides, according to their power on initiation in the polymerization studied is: *o*-Cl > *o*-Me > *p*-OMe > Cinnamoyl > Palmitoyl > *p*-Cl > *m*-Cl > *m*-NO_2 > *p*-NO_2. The different effect of the *meta*- and the *para*-position for chloro- and for nitro-substituents is noteworthy. The very low value of k_i for nitro-substituted peroxides may be due to the formation of stabilized radicals with the monomer itself, and this is more likely in the case of *p*-nitrobenzoyl peroxide. This is confirmed by the retarding effect of *p*-nitrobenzoyl peroxide on polymerization, which is evident from the non-linearity of the plot of R_p against $I^{\frac{1}{2}}$ (Fig. 2).

Our investigations also indicate that the value of k_i (Table 4) changes with the monomer concentration, tending to increase with dilution. Swain *et al.*[8] similarly found that the value of k_i in dioxan solution is higher than that in bulk polymerization. Nandi and Palit [6f] found the same trend in the hydrogen peroxide-initiated polymerization of methyl methacrylate, although at a very high dilution of the monomer the value again decreased, but was still higher than that for bulk. This may be attributed to the fact that in solution the peroxide decomposes more rapidly and so is able to initiate more polymer chains.

Chain-transfer Coefficients.—(1) *To monomer.* The chain-transfer coefficient (C_M) of

[8] Swain *et al.*, *J. Amer. Chem. Soc.*, 1950, **72**, 5426.

growing methyl methacrylate radical to monomer has been calculated from equation (2). For bulk polymerization the equation reduces to

$$1/\bar{P} = C_M + C_I(I/M) + \delta^2 R_p/M^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

and the plot of $1/\bar{P}$ against R_p should give a straight line for those catalysts which have no chain-transfer reaction. From Fig. 6 it is evident that this plot is a straight line only for

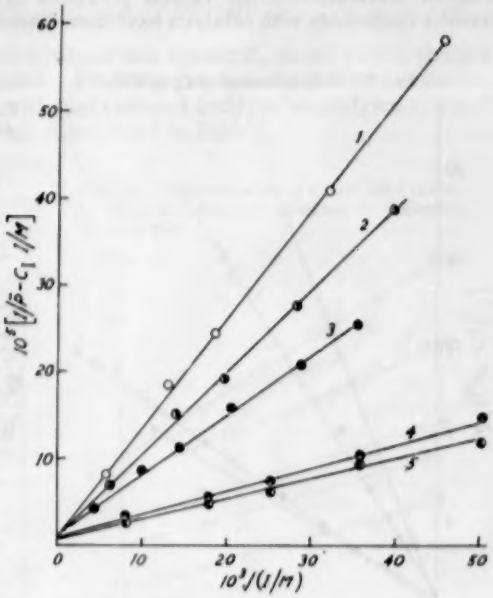


FIG. 5. *Determination of the initiation constant by the degree of polymerization method.*

1, *o*-Chlorobenzoyl peroxide.
2, *o*-Methylbenzoyl peroxide.
3, Palmitoyl peroxide.
4, *m*-Nitrobenzoyl peroxide.
5, *p*-Nitrobenzoyl peroxide.

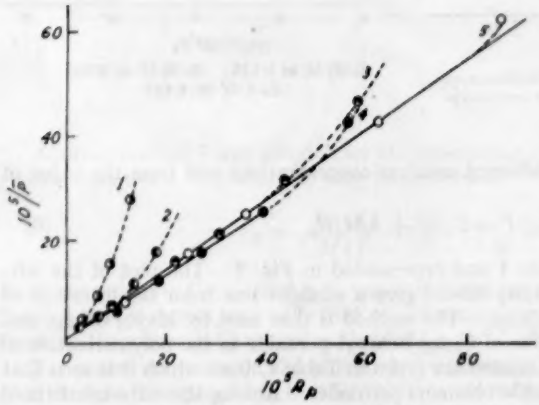


FIG. 6. *Determination of C_M at 60°.*

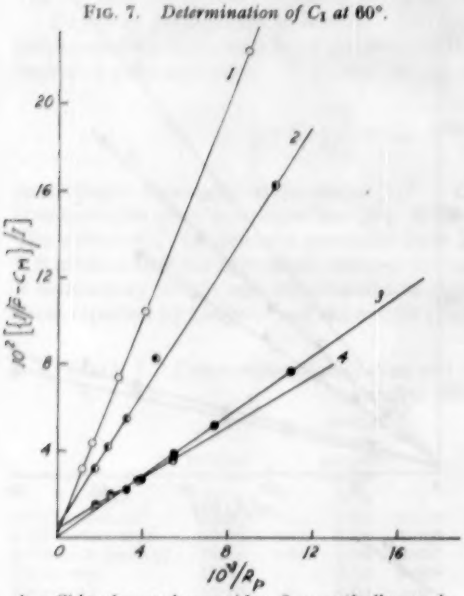
1, *p*-Nitrobenzoyl peroxide.
2, *m*-Nitrobenzoyl peroxide.
3, *o*-Methylbenzoyl peroxide.
4, *p*-Methoxybenzoyl peroxide.
5, *o*-Chlorobenzoyl peroxide.

palmitoyl peroxide, being curved for the other peroxides. The intercept of the straight line for palmitoyl peroxide should give the value of C_M. For the other peroxides C_M was determined from the intercept of the linear part of the curve of the plot at low concentration of the catalyst. The results are included in Table 1. The mean value of C_M obtained is $1{\cdot}03 \times 10^{-5}$, in agreement with the value of $1{\cdot}00 \times 10^{-5}$ reported by Baysal and Tobolsky [6d] and by Nandi *et al.*[9]

[9] Nandi *et al.*, Proceedings of International Symposium on Macromolecules, Milan, 1954, published in *Ricerca Sci.*

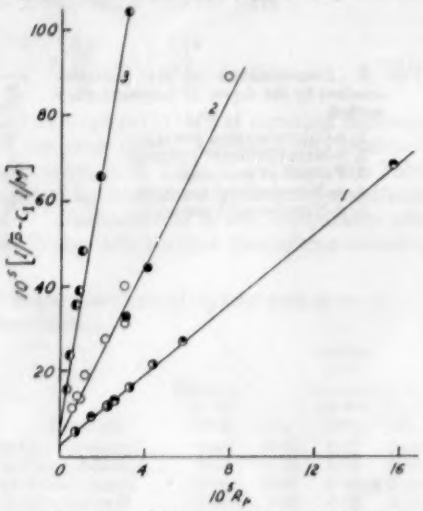
(2) *To catalyst.* The substituents in the benzene ring of the diacyl peroxide have a general inductive effect,[8] depending on their electro-positive or -negative character, on the radical-induced decomposition of the peroxide in solution. Cooper [1] studied the radical-induced decomposition of different diacyl peroxides in styrene and concluded that this decomposition, termed chain-transfer reaction, increases with increasing negativity of the substituents. We have carried out similar experiments to determine the radical-induced decompositions of various peroxides in methyl methacrylate at 60°. Chain-transfer coefficients with catalysts have been determined according to equation (6) from the

FIG. 7. *Determination of C_I at 60°.*



1, *o*-Chlorobenzoyl peroxide; 2, *o*-methylbenzoyl peroxide; 3, palmitoyl peroxide; 4, *p*-methoxybenzoyl peroxide.

FIG. 8. *Determination of C_S for ethyl acetate in polymerization catalyzed by palmitoyl peroxide.*



1, $S/M = 1{\cdot}112$; 2, $S/M = 2{\cdot}594$; 3, $S/M = 4{\cdot}448$.

measured value of $1/\overline{P}$ and R_p at different catalyst concentrations and from the value of C_M just determined:

$$(1/\overline{P} - C_M)/I = C_I/M + k_t M/R_p \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

The results are summarized in Table 1 and represented in Fig. 7. The plot of the left-hand side of equation (6) against $1/R_p$ should give a straight line from the intercept of which the value of C_I can be calculated. The method is that used by Mayo, Gregg, and Matheson [10] for determining the value of C_I for benzoyl peroxide in the polymerization of styrene. The values of C_I thus calculated are given in Table 1, from which it is seen that the order of C_I is *o*- > *p*- > *m*- in chlorobenzoyl peroxides. Among the nitro-substituted peroxides, the *para*-isomer has an inordinately high value for C_I, in conformity with the retarding effect of the nitro-compound probably owing to the resonance stabilisation of free radicals of these peroxides. Although in the polymerisation of styrene, nitro-substituted peroxides do not follow the usual polymerization equation and abnormally high values of C_I are obtained, with methyl methacrylate the value is of normal order. A comparison of the values of C_I for methyl methacrylate and for styrene (Table 5) shows that styrene has a higher transfer constant with catalysts than methyl methacrylate.

[10] Mayo, Gregg, and Matheson, *J. Amer. Chem. Soc.*, 1951, **73**, 1691.

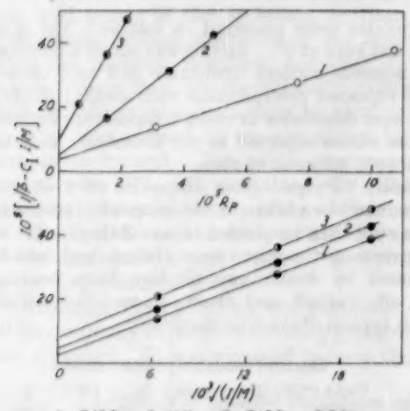
This is due to the structure of the two monomers, methyl methacrylate with an α-methyl group having a higher tendency to add than to undergo transfer reaction.

(3) *To solvent.* The monomer and catalyst transfer coefficients being known, equation (4) can be used for the determination of solvent transfer in catalyzed system. A thorough study was carried out with methyl methacrylate as monomer and ethyl acetate and toluene as solvent at 60°. The general equation (2) can be transformed into :

$$1/\overline{P} - C_I I/M = C_M + C_S S/M + \delta^2 R_p/M^2 \quad . \quad . \quad . \quad . \quad . \quad (7)$$

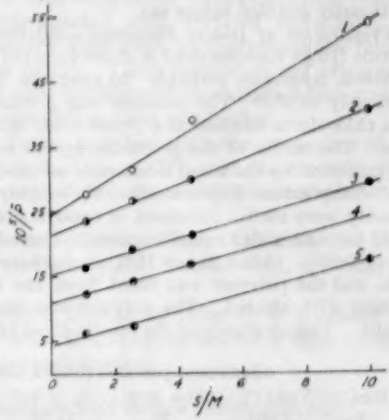
At a constant value of S/M the plot of the left-hand side against R_p should yield a straight line from whose intercept C_S can be evaluated. From experiments with different initiators, the values of C_S so calculated agree well with that obtained from the uncatalyzed system.[4] Some typical results are represented in Figs. 8 and 9 and in Table 2.

FIG. 9. *Determination of C_S for toluene in polymerization catalyzed by o-methylbenzoyl peroxide.*



1, $S/M = 1{\cdot}005$; 2, $S/M = 2{\cdot}340$; 3, $S/M = 4{\cdot}020$.

FIG. 10. *Determination of C_S for ethyl acetate in polymerization catalyzed by palmitoyl peroxide.*



$10^4 I/M$ = (1) 8·43, (2) 4·20, (3) 2·10, (4) 1·05, (5) 0·21.

Another method [7] was adopted for the determination of C_S by direct application of the general equation. Equation (2) may be written as

$$C_S = \frac{1}{S/M}\left\{\frac{1}{\overline{P}} - C_M - C_I\frac{I}{M} - \frac{\delta^2}{M^2}\cdot\right\} \quad . \quad . \quad . \quad . \quad . \quad (9)$$

From the values of C_M, C_I, and δ, C_S was calculated from the equation (9) and it is seen from Table 3 that it agrees well with that of the uncatalyzed one. This gives an independent check on the values of C_S as well as those of C_M and C_I determined previously.

For palmitoyl peroxide the plot of $1/\overline{P}$ against S/M at constant I/M (Fig. 10) gave good straight lines parallel to that for the uncatalyzed reaction up to a certain concentration of the peroxide, but at higher concentrations the slope tended to increase. For *m*-nitrobenzoyl and cinnamoyl peroxide, where the value of k_i is low, we again find that this plot gives the correct value of C_S (Table 3) at low concentrations of the initiator. For solvents where R_p is proportional to M^2 the general equation (2) may be transformed as follows : [7]

$$1/\overline{P} = C_M + C_S(S/M) + C_I(I/M) + \delta\sqrt{k_i}\sqrt{I/M} \quad . \quad . \quad . \quad (9)$$

At a constant value of I/M the plot of $1/\overline{P}$ against S/M for the determination of C_S, as suggested by Mayo *et al.*,[10] should give a correct value only if the last term of equation (9)

is sensibly constant. Allen, Merrett, and Scanlan [11] have used the plot of $(1/\bar{P} - 1/\bar{P}_0)$ against S/M to determine C_S in the catalyzed system, instead of the conventional plot of Mayo *et al.*[10] If R_p is not proportional to M^1, or k_t varies appreciably with dilution, the term will vary with each monomer concentration and in that case Mayo's method would fail in the catalysed system.[7] Since in the present case R_p is directly proportional to M^1 at all monomer concentrations, the rise in the slope of the plot of $1/\bar{P}$ against S/M is most probably due to a large variation of the value of k_t, which has already been found to increase with dilution.

Experimental

Monomer.—Quinol-stabilised methyl methacrylate (National Chemical Laboratory, Poona) was purified by repeated washing with 5% aqueous sodium hydroxide followed by water. After being dried ($CaCl_2$) it was fractionally distilled twice, and the fraction of b. p. 100—100·5° collected. The purity of monomer was found to be 98—99% by the bromine addition method.[12] The absence of peroxide was ascertained by the usual iodometric method.

Solvents.—A.R. and L.R. quality samples were purified by the usual methods, dried, and fractionally distilled before use.

Preparation of Diacyl Peroxides.—All the peroxides were prepared as follows: the acid chloride (10 g.) was dissolved in chloroform (10 c.c.) and kept at 0°. To this was added a mixture of 20-vol. hydrogen peroxide (20 c.c.) and 20% aqueous sodium hydroxide (6·5 c.c.) cooled previously to 0°.[13] The peroxide was purified by repeated precipitation with methyl alcohol from chloroform solution at 0°, then dried in a vacuum desiccator at room temperature for two days. The m. p.s of the peroxides agreed with the values reported in the literature, and the purity, tested by the usual iodometric method, was 99% for most of them.

Polymerization Experiments.—Thoroughly cleaned "Pyrex"-glass ampoules of 5—8 c.c. capacity were used. Solutions of catalysts in monomer were taken in the ampoules, frozen in liquid air, and sealed under vacuum. These tubes were then suspended in an oil-thermostat at 60° (±0·05°). After about 10% of monomer conversion, the tubes were chilled, and broken open, and the polymer was freed from the monomer by double precipitation from benzene solution with alcohol. The polymer was filtered off, washed, and dried *in vacuo* to constant weight. The constancy of the results given below is typical of the reproducibility.

	Cinnamoyl peroxide (0·0272 mole/l.)				Benzoyl peroxide (0·0037 mole/l.)			
Run	Yield (%)	Time (min.)	$R_p \times 10^5$	η	Yield (%)	Time (min.)	$R_p \times 10^5$	η
I	13·08	38	53·29	0·87	7·97	40	30·86	1·50
II	13·13	38	53·30	0·86	7·90	40	30·60	1·50
III	12·9	38	52·80	0·87	7·88	40	30·10	1·505

The degree of polymerization (n) was determined from the relation $n = k[\eta]^{\alpha}$, where $[\eta]$ is the intrinsic viscosity, and K and α are constants equal to $2{\cdot}81 \times 10^{-3}$ and 1·32 respectively in benzene solution.[14] The viscosity measurements were done in benzene solution at 35° by means of Ostwald capillary viscometers, with a flow time for benzene equal to 224·3 sec. and 132·5 sec.

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[11] Allen, Merrett, and Scanlan, *Trans. Faraday Soc.*, 1955, **51**, 95.
[12] Kauffmann and Hartweg, *Ber.*, 1937, **70**, 2554.
[13] Hey and Walker, *J.*, 1948, 2213.
[14] Baxendale *et al.*, *J. Polymer Sci.*, 1946, **1**, 273.

86. *Complexes of Palladium and Platinum with Certain Chelate Compounds.*

By S. E. Livingstone.

The complexes formed by bivalent palladium and platinum with a number of chelate compounds are described. The chelate components employed each contain an acidic group (CO_2H, SH, or OH) and a donor atom (N, S, or As) (some of them new compounds). All these form palladium complexes, but, in a number of cases, no platinum complex was obtained.

In previous investigations (Livingstone, Plowman, and Sorenson, *J. Proc. Roy. Soc., New South Wales*, 1950, **84**, 28; Livingstone and Plowman, *ibid.*, p. 188; 1951, **85**, 116) the palladium complex of *o*-methylthiobenzoic acid was described and also a number of halogen-bridged complexes containing this chelating compound. The purpose of the present work was to ascertain whether bivalent palladium and platinum would form complexes with a number of chelate components. All the organic compounds used contain one acid group in the molecule, so that if they reacted with bivalent palladium, the compounds formed would be of the inner complex type such as diglycinepalladium(II) (Pinkard, Sharrat, Wardlaw, and Cox, *J.*, 1934, 1012). These complexes are of especial interest since they are theoretically capable of forming bridged complexes when treated with palladium salts containing an atom or group which can act as a bridge.

The ligands used by us are shown in the Table, together with the properties of the complexes formed. The acidic groups were CO_2H, SH, or OH, and the co-ordinating groups were NH_2, SR, or $AsMe_2$. It will be seen that palladium yielded a complex in all cases, but platinum in only seven of the thirteen cases.

The ligands marked with an asterisk are new compounds. Their syntheses, and those of the analogues, *o*-propylthio-, *o*-pentylthio-, and *o*-octylthio-benzoic acid, are recorded in the Experimental section.

Although the palladous and platinous complexes formed by these chelate ligands are all theoretically capable of showing geometrical isomerism, only one isomer of each complex was obtained. It was assumed to have the *trans*-configuration.

Complexes of bivalent palladium and platinum with certain chelate groups.

	Pd^{II} complex	Pt^{II} complex
I Anthranilic acid	Yellow; m. p. 245°; i.[1]	Puce; decomp.; i.[1]
II 3-Amino-2-naphthoic acid	Buff; decomp.; i.	Pale yellow; impure
III *o*-Methylthiobenzoic acid	Canary-yellow; m. p. 193°; w; sp.s.[2]	None
IV *o*-*n*-Butylthiobenzoic acid *	Yellow; m. p. 159°; sp.s.	,,
V *o*-Benzylthiobenzoic acid	Canary-yellow; m. p. 169°; sp.s.	,,
VI *o*-Octadecylthiobenzoic acid *	Yellow; m. p. 106—108°; sp.s.	,,
VII 1 : 2-Di-(*o*-carboxyphenylthio)ethane	Orange-brown; decomp.; i.	Pale yellow; decomp.; i.
VIII *o*-Carboxyphenyldimethylarsine	Yellow; m. p. 168°; w; s.[3]	None
IX *o*-Aminophenol	Buff; decomp.; i.	,,
X *o*-Aminobenzenethiol	Buff; decomp.; i.	Deep yellow; impure
XI *o*-Methylthiobenzenethiol *	Pink; m. p. 157°; s.	Deep yellow; m. p. 158°; sp.s.
XII 3-Dimethylarsinopropane-1-thiol *	Orange; m. p. 180°; w; s.	Yellow; m. p. 187°; s.
XIII 3-Ethylthiopropane-1-thiol *	Impure	Yellow; m. p. 168°; i.

[1] Livingstone and Plowman, *loc. cit.*, 1950. [2] Livingstone, Plowman, and Sorenson, *loc. cit.* [3] Grinberg and Kats, *J. Gen. Chem. (U.S.S.R.)*, 1950, **20**, 248.

w, Soluble in water; unless otherwise stated, these complexes are insoluble in water. s., Soluble; sp.s.; sparingly soluble; i., insoluble, in organic solvents such as alcohol, acetone, nitrobenzene, and chloroform.

Experimental

o-n-*Butylthiobenzoic Acid.*—Thiosalicylic acid (30 g.), potassium hydroxide (25 g.), and *n*-butyl bromide (40 g.) were refluxed in absolute alcohol (400 ml.) under nitrogen for 1 hr., then poured into water (1 l.); the mixture was acidified with hydrochloric acid, and filtered.

The *product*, recrystallized from 50% alcohol (300 ml.), had m. p. 100—101° (29·2 g.) (Found: C, 62·9; H, 6·9%; equiv., 210. $C_{11}H_{14}O_3S$ requires C, 62·8; H, 6·7%; equiv., 210). Similarly were prepared o-n-*propylthio*-, m. p. 124° (Found: C, 60·8; H, 5·8%; equiv., 195. $C_{10}H_{12}O_3S$ requires C, 61·2; H, 6·2%; equiv., 196), *o-pentylthio*-, m. p. 104—105° (Found: C, 64·4; H, 7·2%; equiv., 224. $C_{12}H_{16}O_3S$ requires C, 64·3; H, 7·2%; equiv., 224), o-n-*octylthio*-, m. p. 80° (Found: C, 67·6; H, 8·3%; equiv., 266. $C_{15}H_{22}O_3S$ requires C, 67·8; H, 8·4%; equiv., 267), and o-n-*octadecylthio-benzoic acid*, m. p. 101·5° (Found: C, 73·7; H, 10·3%; equiv., 408. $C_{25}H_{42}O_3S$ requires C, 73·8; H, 10·4%; equiv., 406).

1 : 2-*Di*-(o-*carboxyphenylthio*)*ethane*.—An alcoholic solution (500 ml.) of thiosalicylic acid (20 g.), potassium hydroxide (16 g.), and ethylene dibromide (12·2 g.) was refluxed under nitrogen for 90 min., then poured into water and acidified with hydrochloric acid. The white precipitate was filtered off and dried (yield, 18·5 g.). The *product* was not appreciably soluble in hot alcohol, benzene, acetone, or ether, but readily soluble in hot pyridine. Recrystallized from pyridine, it yielded colourless elongated prisms (14·8 g.), m. p. 297° (Found: C, 57·7; H, 4·3%; equiv., 166. $C_{16}H_{14}O_4S_2$ requires C, 57·5; H, 4·2%; equiv., 167).

Synthesis of o-*Methylthiobenzenethiol*.—o-*Methylthioaniline*. The following preparation is more satisfactory than that described by Hofmann (*Ber.*, 1887, **20**, 1788). *o*-Mercaptoaniline (30 g.) was treated in alcohol (125 ml.) with sodium (5·4 g.) in small pieces. Methyl iodide (33 g.) was added and the whole refluxed for 40 min., then cooled and poured into water (1 l.). The oil, extracted in ether, was dried, recovered by evaporation, and distilled. The sulphide (20·3 g.) had b. p. 126—128°/15 mm., n_D^{17} 1·6264. Beilstein's "Handbuch," Vol. XIII, p. 297, and Suppl. I, p. 124, lists 133°/15 mm., n_D^{17} 1·6263.

o-Methylthiobenzenethiol. *o*-Methylthioaniline (10·3 g.) was diazotized with dilute sulphuric acid (40 ml.) and sodium nitrite (5·7 g.) at 5—8° and added, with stirring, to a solution of sodium ethyl xanthate (40 g.) in water (100 ml.), at 75—85°, during 15 min. The reaction was very violent at the beginning, nitrogen being evolved immediately and a red oil separating. Finally, the mixture was warmed at 90° for 10 min. and then cooled. The red oil was separated, and the aqueous layer was extracted with ether and the ether evaporated. The two lots of oil were combined and refluxed with alcohol (120 ml.) containing potassium hydroxide (17 g.) for 2½ hr. The red liquor was filtered to yield a considerable quantity of white crystals. The filtrate was concentrated to 45 ml., then poured into water (500 ml.), and the crystals were added to this mixture. The resulting solution was acidified with hydrochloric acid and extracted with ether, and the extracts were washed with water and dried. After evaporation of the ether, the crude oil (12·3 g.) was distilled under reduced pressure in an atmosphere of coal gas. Considerable decomposition occurred during the distillation, leaving a tarry residue. The water-white fraction (b. p. 100—105°/2 mm.; 2·4 g.) was collected. This *thiol* gave a positive test for thiol with alkaline sodium nitroprusside (Found: C, 54·1; H, 5·1. $C_7H_8S_2$ requires C, 53·8; H, 5·2%).

Preparation of 3-*Dimethylarsinopropane*-1-*thiol*.—3-Chloropropyldichloroarsine, prepared as described by Gough and King (*J.*, 1928, 2439), had b. p. 132—136°/25 mm. 3-Chloropropyldimethylarsine, prepared by Barclay and Nyholm's method (*Chem. and Ind.*, 1953, 378), had b. p. 59—62°/10 mm. (Found: C, 32·9; H, 6·4. Calc. for $C_5H_{12}ClAs$: C, 32·9; H, 6·6%).

An alcoholic solution of sodium hydrogen sulphide was prepared by dissolving sodium (7·7 g.) in absolute alcohol (300 ml.), and passing hydrogen sulphide into the solution until it was colourless to phenolphthalein. This was added gradually to a solution of 3-chloropropyldimethylarsine (60 g.), in alcohol (50 ml.), in an atmosphere of coal gas. Little reaction took place until the mixture was heated, whereupon sodium chloride was precipitated. The mixture was refluxed for 30 min., then cooled, and filtered. The alcohol was distilled off and the residue was distilled under reduced pressure (coal gas), yielding 3-*dimethylarsinopropane*-1-*thiol* (26·0 g.), b. p. 54—58°/3 mm., n_D^{20} 1·5296 (Found: C, 33·2; H, 7·1. $C_5H_{13}SAs$ requires C, 33·3; H, 7·3%). The compound gives a violet colour with alkaline sodium nitroprusside. The water-white liquid showed no coloration or precipitation when kept under coal gas in a refrigerator for 2 years.

3-*Ethylthiopropane*-1-*thiol*.—To a solution from sodium (30 g.) in alcohol (500 ml.) was added ethanethiol (75 g.) in alcohol (100 ml.), followed by 3-chloropropan-1-ol (114 g.) during 10 min. Sodium chloride separated and the temperature rose to about 60°. When the addition was complete, the mixture was refluxed for 1½ hr., then filtered and evaporated. Distillation in coal gas *in vacuo* gave water-white 3-*ethylthiopropan*-1-*ol* (86·2 g.), b. p. 98—99°/10 mm., n_D^{20} 1·4843 (Found: C, 50·2; H, 10·1. $C_5H_{12}OS$ requires C, 50·0; H, 10·1%).

This alcohol (85·5 g.) was treated in ligroin with thionyl chloride during 15 min., then refluxed for 1½ hr., after which no more hydrogen chloride was evolved. About 3 g. of black oil were

formed, which was discarded. The ligroin was distilled off and the product distilled, yielding *3-ethylthiopropyl chloride* (75 g.), b. p. 65—66°/10 mm., n_D^{20} 1·4843 (Found: C, 43·5; H, 8·0. $C_5H_{11}SCl$ requires C, 43·3; H, 8·0%).

Sodium ethyl sulphide, prepared as before, from sodium (37·5 g.) and alcohol (500 ml.), was treated gradually with the preceding chloride (225 g.), and the whole refluxed for 30 min. Hydrochloric acid was added until the mixture was just acid. The sodium chloride was filtered off, and the alcohol removed by distillation at the water pump. Distillation under reduced pressure gave *3-ethylthiopropane-1-thiol* (179 g.), b. p. 47°/1 mm., n_D^{23} 1·5135 (Found: C, 44·2; H, 8·7. $C_5H_{12}S_2$ requires C, 44·1; H, 8·9%). The colourless product gave a violet colour with alkaline sodium nitroprusside.

Bis-3-amino-2-naphthoatopalladium(II).—To 3-amino-2-naphthoic acid (1·05 g.), dissolved in one equivalent of sodium hydroxide solution (50 ml.), at 60°, was added potassium chloropalladate(II) (0·9 g.), dissolved in water (20 ml.). There was an immediate precipitation of the buff-coloured *palladium complex*, which was filtered off, washed with hot water, then acetone, and dried at 120° (Found: C, 55·3; H, 3·5; Pd, 22·5. $C_{22}H_{14}O_4N_2Pd$ requires C, 55·2; H, 3·4; Pd, 22·3%).

A solution of potassium chloroplatinate(II), similarly treated, gave after a few minutes impure yellow crystals.

Bis-(o-n-butylthiobenzoato)palladium(II).—*o-n*-Butylthiobenzoic acid (2·5 g.), in one equivalent of sodium hydroxide solution (50 ml.), was treated with an aqueous solution of potassium chloropalladate(II) (1·9 g.) at room temperature. An oil separated, which crystallized. The product was filtered off and recrystallized from 50% aqueous acetone. Fine yellow crystals (2·0 g.) of the *palladium complex* were obtained, having m. p. 159° (Found: C, 49·5; H, 4·9; Pd, 20·4. $C_{22}H_{26}O_4S_2Pd$ requires C, 50·3; H, 5·0; Pd, 20·3%). The conductivity of the complex at 25° was: in nitrobenzene, $\Lambda_{1000} = 0{\cdot}03$ mho; in water, $\Lambda_{2000} = 11$ mho.

Bis-(o-benzylthiobenzoato)palladium(II).—A solution of potassium chloropalladate(II) (9·75 g.) in water (100 ml.) was slowly poured into a boiling aqueous solution (200 ml.) containing *o*-benzylthiobenzoic acid (14·6 g.) and sodium hydroxide (2·4 g.). The immediate yellowish-orange precipitate was filtered off and recrystallized from 60% aqueous acetone (2·5 l.). The recrystallized complex was washed with acetone and dried over phosphoric oxide. The bright yellow prisms (16 g.) are soluble in chloroform and moderately soluble in aqueous acetone, and melt at 169° (with decomp.) (Found: C, 56·5; H, 3·8; Pd, 18·0. $C_{28}H_{22}O_4S_2Pd$ requires C, 56·7; H, 3·7; Pd, 18·0%). Λ_{2000} in nitrobenzene at 25° = 0.

Bis-(o-octadecylthiobenzoato)palladium(II).—*o*-Octadecylthiobenzoic acid (2·0 g.) was dissolved in one equiv. of 0·1M-sodium hydroxide and the solution diluted to 150 ml. Potassium chloropalladate(II) (0·8 g.), in water (40 ml.), was added at 90°. A pale yellow turbid liquor resulted. On being heated with acetone (75 ml.) for several minutes, the precipitate became granular, and, after the solution had cooled, the complex was filtered off and washed first with water, then with acetone, in which it was slightly soluble (2·1 g.; m. p. 106—108°) (Found: C, 65·5; H, 9·1; Pd, 11·6. $C_{50}H_{82}O_4S_2Pd$ requires C, 65·4; H, 9·1; Pd, 11·6%). Λ_{2000} in nitrobenzene = 0·2 mho.

1 : 2-Di-(*o-carboxyphenylthio*)*ethanepalladium*(II).—1 : 2-Di-(*o*-carboxyphenylthio)ethane (1 g.) was treated with one equiv. of 0·5M-sodium hydroxide, and the small amount of undissolved organic acid was filtered off. The filtrate was poured into a solution of potassium chloropalladate(II) (1 g.) in hot water (15 ml.). A crystalline precipitate was formed immediately. After being heated on the steam-bath for a further 15 min., the mixture was filtered, and the orange crystals were washed with hot water, then acetone. The *complex* (1·15 g.) is practically insoluble in water and organic solvents (Found: C, 42·9; H, 2·7; Pd, 24·6. $C_{16}H_{12}O_4S_2Pd$ requires C, 43·8; H, 2·8; Pd, 24·3%).

1 : 2-Di-(*o-carboxyphenylthio*)*ethaneplatinum*(II).—1 : 2-Di-(*o*-carboxyphenylthio)ethane (1 g.), dissolved in one equiv. of 0·5M-sodium hydroxide, was added to a solution of potassium chloroplatinate(II) (1·25 g.) in hot water (15 ml.). No precipitation occurred but, on the addition of one drop of dilute acetic acid, a cream-coloured precipitate was formed. The mixture was digested on the water-bath for 15 min. and the *platinum complex* was then filtered off and washed with water and acetone (yield, 1·12 g.) (Found: C, 36·2; H, 2·3; Pt, 36·7. $C_{16}H_{12}O_4S_2Pt$ requires C, 36·4; H, 2·3; Pt, 37·0%).

Bis-o-aminophenolpalladium(II) *Monohydrate*.—*o*-Aminophenol (1 g.) was dissolved in water (40 ml.), containing sodium hydroxide (0·3 g.); to this was added potassium chloropalladate(II) (1·5 g.) in water (30 ml.). The buff-coloured complex, which was immediately precipitated, was washed with hot water, then acetone (in which it is virtually insoluble) and dried *in vacuo*

over phosphoric oxide (Found : C, 42·2; H, 3·8; N, 8·3; Pd, 31·2. $C_{12}H_{12}O_2N_2Pd,H_2O$ requires C, 42·3; H, 4·1; N, 8·2; Pd, 31·2%).

No precipitate or colour change occurred when potassium chloroplatinate(II) was used in this reaction.

Bis-o-aminobenzenethiolpalladium(II).—*o*-Aminobenzenethiol (1 g.) was treated with one equiv. of 0·5M-sodium hydroxide and then an aqueous solution of potassium chloropalladate(II) (1·25 g.). A chocolate-coloured amorphous precipitate was formed which, on being boiled for some time with aqueous acetone, became crystalline and much paler. The buff-coloured crystals (1·22 g.) were washed with hot water, then acetone. The *compound* is insoluble in water and organic solvents (Found : C, 40·7; H, 3·4; Pd, 30·2. $C_{12}H_{12}N_2S_2Pd$ requires C, 40·6; H, 3·4; Pd, 30·1%).

Potassium chloroplatinate(II), similarly treated, gave impure yellow crystals, which became green when kept in a dessicator for several days.

Bis-o-methylthiobenzenethiolpalladium(II).—*o*-Methylthiobenzenethiol (0·6 g.) was treated with one equiv. of 0·5M-sodium hydroxide and an aqueous solution (10 ml.) of potassium chloropalladate(II) (0·64 g.). An amorphous product was precipitated, but after the mixture had been heated for some time the precipitate crystallized. The pink *complex* (0·61 g.), m. p. 157°, is soluble in acetone to a pinkish-purple solution, and in chloroform and nitrobenzene to yield red solutions (Found : C, 40·2; H, 3·3; Pd, 25·3. $C_{14}H_{14}S_4Pd$ requires C, 40·3; H, 3·4; Pd, 25·6%). Conducitivity at 25° : in acetone, $\Lambda_{500} = 0{\cdot}06$ mho; in nitrobenzene, $\Lambda_{500} = 0{\cdot}02$ mho.

Bis-o-methylthiobenzenethiolplatinum(II).—A solution of potassium chloroplatinate(II) (0·52 g.) in water (10 ml.) was added to a suspension of *o*-methylthiobenzenethiol (0·39 g.) in one equiv. of 0·5M-sodium hydroxide. After a few minutes, fine yellow crystals were slowly precipitated. The *product* was filtered off and heated with a small quantity of acetone. The compound (0·31 g.), m. p. 158°, is moderately soluble in acetone and nitrobenzene (Found : C, 32·8; H, 2·7; Pt, 38·6. $C_{14}H_{14}S_4Pt$ requires C, 33·2; H, 2·8; Pt, 38·6%). Conductivity at 25° : in acetone, $\Lambda_{1000} = 0{\cdot}06$ mho; in nitrobenzene, $\Lambda_{1000} = 0{\cdot}01$ mho.

Bis-(3-dimethylarsinopropane-1-thiol)palladium(II).—A solution of potassium chloropalladate(II) (1·25 g.) in water (15 ml.) was added slowly, with stirring, to a suspension of 3-dimethylarsinopropane-1-thiol (2·1 g.) in one equiv. of 0·5M-sodium hydroxide. Orange crystals were precipitated, but they were contaminated with excess of thiol. The precipitate was filtered off and washed with water, then acetone, and recrystallized from acetone. The *complex* (1·38 g.), m. p. 180°, is moderately soluble in water and acetone, readily soluble in chloroform, benzene, and nitrobenzene (Found : C, 25·9; H, 5·1; Pd, 23·1%; *M*, cryoscopically in 0·42% nitrobenzene solution, 467; in 0·28% nitrobenzene solution, 477; in 0·37% benzene solution, 465. $C_{16}H_{34}S_2As_2Pd$ requires C, 25·8; H, 5·3; Pd, 23·0%; *M*, 465). Conductivity at 25° : in water, $\Lambda_{1000} = 7$ mho; in nitrobenzene, $\Lambda_{1000} = 0{\cdot}1$ mho.

Bis-(3-dimethylarsinopropane-1-thiol)platinum(II).—A solution of potassium chloroplatinate(II) (2·0 g.), as in the preceding experiment, gave a *complex* which after final trituration with ligroin and recrystallization from 90% acetone (125 ml.) yielded yellow crystals (1·2 g.), m. p. 187° (Found : C, 21·8; H, 4·2. $C_{16}H_{34}S_2As_2Pt$ requires C, 21·7; H, 4·4%). Conductivity in nitrobenzene at 25° : $\Lambda_{1000} = 0{\cdot}1$ mho.

Bis(-3-ethylthiopropane-1-thiol)platinum(II).—The thiol (5·05 g.) was treated with one equiv. of 0·5M-sodium hydroxide and then an aqueous solution of potassium chloroplatinate(II) (7·5 g.) with vigorous stirring. The red colour disappeared from the solution and a yellow oil, which gradually became crystalline, was produced. The crude product was filtered off, washed with water, then boiled with acetone, and collected. The yellow crystals (4·92 g.) are insoluble in water, acetone, chloroform, and nitrobenzene. The *compound* softens at about 145° and melts at 167° to a pale amber liquid which does not decompose below 250° (Found : C, 25·2; H, 4·6; Pt, 42·4. $C_{10}H_{22}S_4Pt$ requires C, 25·8; H, 4·7; Pt, 41·9%).

Potassium chloropalladate(II) gave only a yellow amorphous precipitate.

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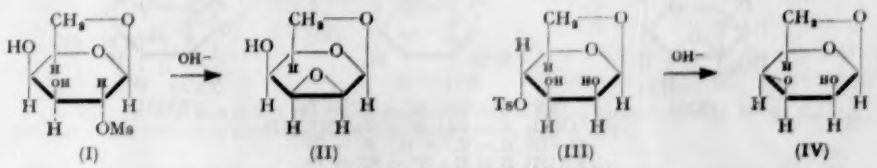
87. O-*Toluene*-p-*sulphonyl Derivatives of* 1 : 6-*Anhydro*-β-D-*altrose and their Behaviour towards Alkali.**

By F. H. Newth.

1 : 6-Anhydro-2-*O*-toluene-*p*-sulphonyl- and 1 : 6-anhydro-3 : 4-di-*O*-toluene-*p*-sulphonyl-β-D-altrose resist conversion into epoxides. 1 : 6-Anhydro-3-*O*-toluene-*p*-sulphonyl-β-D-altrose, prepared by selective acylation of the equatorial hydroxyl group in 1 : 6-anhydro-2-*O*-benzoyl-β-D-altrose, reacts but gives 1 : 6-3 : 4-dianhydro-β-D-altrose rather than 1 : 6-2 : 3-dianhydro-β-D-mannose. The conformational aspects of epoxide formation are considered.

It is well known that a sugar epoxide is formed easily and in good yield by alkaline hydrolysis of a sulphonyloxy-group vicinal to a *trans*-hydroxy-group. However, two derivatives of 1 : 6-anhydro-β-D-altrose containing the *trans*-hydroxy-*O*-toluene-*p*-sulphonyl system have now been found which are inert. The only hexose anhydrides so far known which possess a 1 : 6-anhydro-ring in addition to the epoxide group are 1 : 6-2 : 3- and 1 : 6-3 : 4-dianhydro-β-D-talose (II and IV). They are readily formed from 1 : 6-anhydro-2-*O*-methanesulphonyl-β-D-galactose (I) and 1 : 6-anhydro-4-*O*-toluene-*p*-sulphonyl-β-D-mannose (III) (James, Smith, Stacey, and Wiggins, *J.*, 1946, 625; Hann and Hudson, *J. Amer. Chem. Soc.*, 1942, **64**, 925, 2435), and cleavage of either by alkali gives a mixture in which that isomer predominates whose configuration has the diaxial relationship. A primary objective of this work was to provide further examples in this series to support the general application of Fürst and Plattner's rule to the fission of sugar epoxides (Mills, cited by Newth and Homer, *J.*, 1953, 989; see also Bose, Chaudhuri, and Bhattacharyya, *Chem. and Ind.*, 1953, 869; Newth, *ibid.*, p. 1257; Cookson, *ibid.*, 1954, 223, 1512; Angyal, *ibid.*, p. 1230). Success in this was limited to one other dianhydro-β-D-hexose, but the properties of the sulphonic esters of 1 : 6-anhydro-β-D-altrose mentioned above have necessitated a fuller consideration of the geometry of epoxide formation.



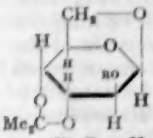
(I) (II) (III) (IV)

(Ms = $CH_3 \cdot SO_2$; Ts = p-$C_6H_4Me \cdot SO_2$)

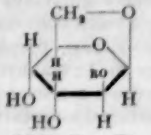
A convenient source of substituted altrose derivatives is 1 : 6-anhydro-3 : 4-*O*-*iso*-propylidene-β-D-altrose (V) (Newth and Wiggins, *J.*, 1950, 1734). This is easily acylated and the 2-*O*-toluene-*p*-sulphonyl (VI) and the 2-*O*-methanesulphonyl derivative (VII) are hydrolysed to the corresponding sulphonyl derivatives (VIII and IX) of 1 : 6-anhydro-β-D-altrose under mildly acidic conditions. Each of these compounds has the correct configuration for epoxide formation and would be expected to yield 1 : 6-2 : 3-dianhydro-β-D-allose (X) on treatment with alkali. They were, however, recovered unchanged after being subjected to hot alkoxide or hydroxide as is usually employed—1 : 6-anhydro-2-chloro-2-deoxy-β-D-altrose (Newth and Wiggins, *loc. cit.*) showed a similar resistance. By prolonged and vigorous treatment with sodium methoxide 1 : 6-anhydro-2-*O*-toluene-*p*-sulphonyl-β-D-altrose gave an intractable resin; under such conditions, any epoxide (X) would certainly be decomposed, and the conformation (VIIIa) would also permit a concerted displacement of the type observed by Henbest and Clayton (*Chem. and Ind.*, 1953, 1315) with 3β-*O*-toluene-*p*-sulphonyloxycholestan-5α-ol and 3α-*O*-toluene-*p*-sulphonyloxycoprostan-5β-ol, and by Smith (*ibid.*, 1955, 92) in the formation of 2-deoxy-D-ribose from 3-*O*-methanesulphonyl-D-glucopyranose (XI).

* Part of this work was communicated at the Amer. Chem. Soc. 126th Meeting, New York, September, 1954.

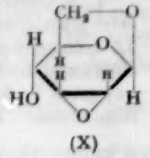
A potential intermediate for the formation of 1 : 6-2 : 3-dianhydro-β-D-mannose (XII) was prepared by the following sequence. 1 : 6-Anhydro-2-*O*-benzoyl-3 : 4-*O*-*iso*propylidene-β-D-altrose (XIII), formed nearly quantitatively from the 2-hydroxy-compound (V), was converted by mild acid into 1 : 6-anhydro-2-*O*-benzoyl-β-D-altrose (XIV). When this was treated with toluene-*p*-sulphonyl chloride in pyridine, 1 : 6-anhydro-2-*O*-benzoyl-3 : 4-di-*O*-toluene-*p*-sulphonyl-β-D-altrose (XV) was formed, together with some of the 3-toluene-



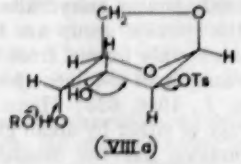
(V) R = H
(VI) R = Ts
(VII) R = Ms
(XIII) R = Bz



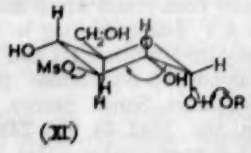
(VIII) R = Ts
(IX) R = Ms
(XIV) R = Bz



(X)

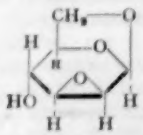


(VIIIa)

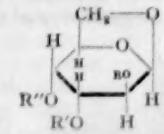


(XI)

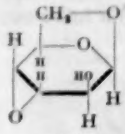
p-sulphonate (XVI). The latter was the sole product when only one mol. of sulphonyl chloride in dilute pyridine at 0° was employed. Sodium methoxide in methanol at 18° removed only the benzoyl group, giving 1 : 6-anhydro-3-*O*-toluene-*p*-sulphonyl-β-D-altrose (XVII), which was not oxidised by sodium metaperiodate, showing the toluene-*p*-sulphonyl group to be at position 3.



(XII)



(XV) R = Bz; R′ = R″ = Ts
(XVI) R = Bz; R′ = Ts; R″ = H
(XVII) R = R″ = H; R′ = Ts
(XXIII) R = H; R′ = R″ = Ts



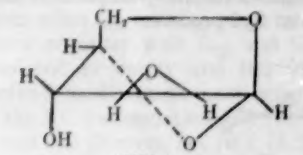
(XVIII)

The preferential formation of the 3-toluene-*p*-sulphonate might be expected since the 3-hydroxyl group in 1 : 6-anhydro-2-*O*-benzoyl-β-D-altrose is equatorial and that at $C_{(4)}$ is axial (cf. VIII*a*). An equatorial is esterified faster than an axial hydroxyl group since, in the latter case, the transition state is subject to more steric hindrance. de la Mare (in Klyne's " Progress in Stereochemistry," Vol. I, Butterworths Ltd., London, 1954, p. 61) has pointed out that this applies specifically to the formation of carboxylates and the formation of a sulphonic ester might be subject to different influences but the example here given suggests that this is not so.

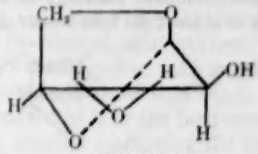
1 : 6-Anhydro-3-*O*-toluene-*p*-sulphonyl-β-D-altrose was unaffected by one mol. of sodium methoxide in boiling methanol after 4 hr. but with higher alkoxide concentration, a low yield of a dianhydrohexose, $C_6H_8O_4$, was obtained. Intramolecular displacement of the toluene-*p*-sulphonate anion from $C_{(3)}$ by the hydroxyl anion at $C_{(2)}$ must lead to the formation of 1 : 6-2 : 3-dianhydro-β-D-mannose (XII) but a second intramolecular nucleophilic displacement by the 4-hydroxyl group which is *trans* to the 2 : 3-epoxide group is possible. The dianhydride therefore could be either (XII) or 1 : 6-3 : 4-dianhydro-β-D-altrose (XVIII) and its identity was decided by fission of the epoxide ring. The isomer (XII) would give derivatives of D-altrose and D-glucose whereas the 1 : 6-3 : 4-dianhydride (XVIII) would give derivatives of D-idose and D-mannose. In each case D-glucose and D-mannose would be expected to predominate since these have the diaxial relationship when the 1 : 6-ring is

retained. Treatment with sodium hydroxide gave an ambiguous result since the interconversion (XII) ⇌ (XVIII) is possible. Dilute sulphuric acid on the other hand gave only one product which paper chromatography showed to be either 1 : 6-anhydro-β-D-glucose or 1 : 6-anhydro-β-D-mannose (the hydrolytic conditions did not open the 1 : 6-anhydro-ring), and a distinction in favour of 1 : 6-anhydro-β-D-mannose was made by paper ionophoresis. The compound, $C_6H_8O_4$, is therefore 1 : 6-3 : 4-dianhydro-β-D-altrose and acidic fission of its epoxide yields mainly the diaxial isomer in conformity with Fürst and Plattner's rule.

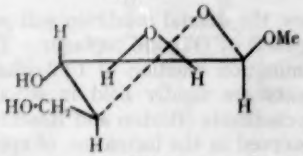
Examples of this isomerisation are already known. Lake and Peat (*J.*, 1939, 1069) found that the chief product, methyl 2 : 3-anhydro-β-D-mannopyranoside (XIX), from the reaction of methyl 2-*O*-toluene-*p*-sulphonyl-β-D-glucopyranoside with sodium methoxide



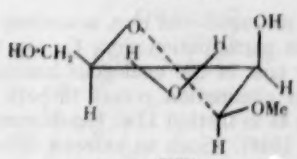
(XII*a*)



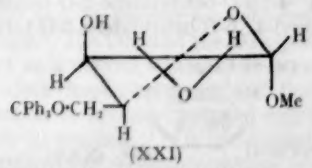
(XVIII*a*)



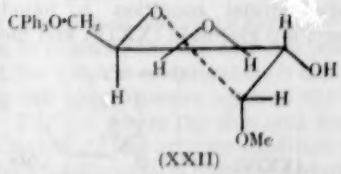
(XIX)



(XX)



(XXI)



(XXII)

(In XVIII*a*, XX, and XXII the tetrahydropyran ring is shown rotated through 60° to the right. Because of the half-chair conformation, all groups will be either e′ or a′.)

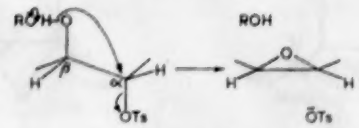
is always accompanied by some methyl 3 : 4-anhydro-β-D-altropyranoside (XX). More recently Buchanan (*Chem. and Ind.*, 1954, 1484) showed that methyl 2 : 3- (XXI) and 3 : 4-anhydro-6-*O*-trityl-α-D-galactopyranoside (XXII) are formed from methyl 4-*O*-toluene-*p*-sulphonyl-6-*O*-trityl-α-D-glucoside by alkali. There is at present no indication as to which epoxide predominates in this reaction mixture. [A similar intramolecular process accounts for the formation of methyl 3 : 6-anhydro-β-D-gluco-furanoside and -pyranoside from methyl 2 : 3-anhydro-β-D-allo-furanoside and -pyranoside (Ohle and Wilcke, *Ber.*, 1938, **71**, 2316; Peat and Wiggins, *J.*, 1938, 1088; see also Peat, *Adv. Carbohydrate Chem.*, 1946, **2**, 51).]

It is important to consider the factors which could determine the direction of these interconversions. The conformations of the three pairs of isomers are shown in their respective formulæ and it is perhaps significant that the chief product (XVIII*a* and XIX) in the first two pairs is that in which the free hydroxyl group is equatorial. This suggests that the conformation determines which isomer will predominate inasmuch as the epoxide group is attacked more easily by an axial than by an equatorial hydroxyl group. On this basis one would expect methyl 3 : 4-anhydro-6-*O*-trityl-α-D-galactoside to be the chief product in the mixture (XXI, XXII). Nucleophilic activity of the 2- and 4-hydroxyl groups must also be considered and that at $C_{(2)}$, with its neighbouring aldehydic $C_{(1)}$, will be subject to an electronic pull by that centre. Its anion will consequently have reduced nucleophilic character relative to that at $C_{(4)}$ and would be less inclined to attack the

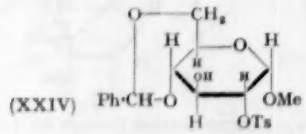
neighbouring epoxide. If this were a primary effect it would mean that a 3 : 4-epoxide should always be the chief product, but the predominance of (XIX) over (XX) contradicts this. In the absence of reaction rates and reliable product analysis no more can be said at present than that conformation appears to exert the greater influence.

To return to the behaviour of the 3-*O*-toluene-*p*-sulphonyl group attached to 1 : 6-anhydro-β-D-altrose, it was found that in contrast to (XVII), 1 : 6-anhydro-3 : 4-di-*O*-toluene-*p*-sulphonyl-β-D-altrose (XXIII) was unaffected by sodium methoxide in boiling methanol for 20 hr. In order to rationalise the inertness of (XXIII) and 1 : 6-anhydro-2-*O*-toluene-*p*-sulphonyl-β-D-altrose compared with 1 : 6-anhydro-3-*O*-toluene-*p*-sulphonyl-β-D-altrose, it is necessary to consider general conformational aspects of the formation of sugar epoxides.

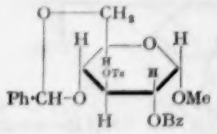
The base-catalysed reaction of a *trans*-1 : 2-diol mono-*O*-toluene-*p*-sulphonate to give an epoxide is almost certain to involve an intramolecular S_N2 process :



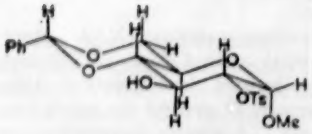
and in a six-membered ring, according to present views, the diaxial condition will permit maximum participation since C_α, C_β, the O of OH and O of OTs are coplanar. This is certainly true in the analogous bimolecular ionic elimination reaction of 1 : 2-dihalides, where no elimination occurs if both *trans*-substituents are rigidly held in equatorial positions as in methyl 11α : 12β-dibromo-3α : 9β-epoxycholanate (Barton and Rosenfelder, *J.*, 1951, 1048). Such an extreme difference is not observed in the formation of epoxides in the carbohydrate field where both diequatorial and diaxial systems react smoothly. The diequatorial condition is found in methyl 4 : 6-*O*-benzylidene-2-*O*-toluene-*p*-sulphonyl-α-D-glucoside (XXIV) and methyl 2-*O*-benzoyl-4 : 6-*O*-benzylidene-3-*O*-toluene-



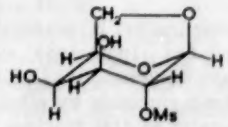
(XXIV)



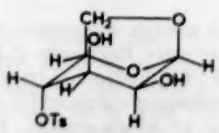
(XXV)



(XXIVa)



(Ia)



(IIIa)

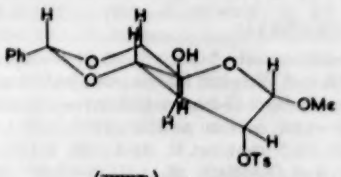
p-sulphonyl-α-D-glucoside (XXV) which give the 2 : 3-*manno*- and 2 : 3-*allo*-epoxide (Robertson and Griffith, *J.*, 1935, 1193). [It should be noted that in (XXV) the 2-*O*-benzoyl group is directly hydrolysed and does not participate in the reaction as it would under acidic solvolytic conditions (Winstein, Hanson, and Grunwald, *J. Amer. Chem. Soc.*, 1948, **70**, 812).] The esters (XXIV) and (XXV) are formed by selective acylation at $C_{(2)}$ of methyl 4 : 6-*O*-benzylidene-α-D-glucoside, a compound in which the C 1 conformation has been demonstrated by Reeves (*J. Amer. Chem. Soc.*, 1949, **71**, 215) and the *trans*-ring junction makes this a rigid structure about $C_{(4)}/C_{(5)}$ as shown in (XXIV*a*).

The diaxial condition is found in 1 : 6-anhydro-2-*O*-methanesulphonyl-β-D-galactose (I*a*) and 1 : 6-anhydro-4-*O*-toluene-*p*-sulphonyl-β-D-mannose (III*a*) where the 1 C conformation is held firm by the 1 : 6-anhydro-ring. Even in the absence of quantitative data, the preparative conditions employed show that the esters (I) and (III) are converted more easily into epoxides than are (XXIV) and (XXV) although the latter pair must not be

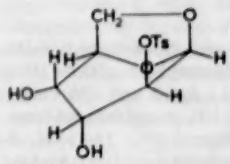
considered inert. There is, unfortunately, no 2- or 3-*O*-toluene-*p*-sulphonyl derivative of methyl 4 : 6-*O*-benzylidene-α-D-altroside (diaxial) for comparison with (XXIV) and (XXV), but a partial comparison shows that methyl 4 : 6-*O*-benzylidene-2-deoxy-2-iodo-α-D-altroside (Richards and Wiggins, *J.*, 1953, 2442) is very easily converted into the 2 : 3-*allo*-epoxide.

Ottar (*Acta Chem. Scand.*, 1947, **1**, 283) has shown by election diffraction that 1 : 2-epoxy*cyclo*hexane has a half-chair conformation similar to that of *cyclo*hexene, and Cookson (*loc. cit.*) first portrayed sugar epoxides in this way, illustrated here by the series (XII*a*, XVIII*a*—XXII). [Reeves (*J. Amer. Chem. Soc.*, 1950, **72**, 1499) stated erroneously that epoxides can only be accommodated in a boat form of the pyranose ring; this would be impossible in compounds such as (II) and (IV)].

There is no difficulty in envisaging the process of 2 : 3-epoxide formation from a diaxial system when $C_{(2)}$ and $C_{(3)}$ move in opposite directions to acquire trigonal character and so become coplanar with $C_{(1)}$ and $C_{(4)}$. Reaction in the diequatorial system cannot be formulated so simply and Barton and Rosenfelder's finding (*loc. cit.*) suggests that a structural modification must occur before reaction. Models show that the C 1 (XXIV*a*) and the 1 C conformation and (VIII*a*) are easily transformed into the boat conformations B 2 and 3 B (Reeves, *loc. cit.*), (XXIV*b*) and (VIII*b*), without disturbing the point of ring



(XXIV*b*)



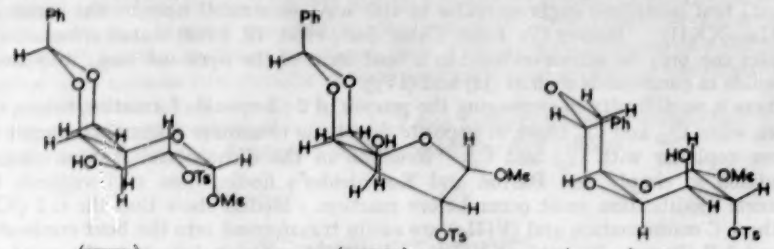
(VIII*b*)

fusion and, by comparison with *cyclo*hexane, only about 5 kcal. should be necessary for this change. The OH and the OTs group are seen to be coplanar and are now in a position to react as a diaxial system. It is recognised that the epoxide conformation is half-way in the chair–boat conversion and that $C_{(2)}$ and $C_{(3)}$ will have to move again in the reverse direction to become coplanar with $C_{(1)}$ and $C_{(4)}$. For this reason the true boat form may never be reached. It is convenient, however, to formulate this extreme condition since in its attainment steric interactions are apparent which readily explain different activities and permit predictions. In passing from chair to boat conformation there will be steric interaction between vicinal groups when one is axial and the other equatorial since they will have to move past each other. In the final boat form there will be interaction between1 : 2-, 1 : 3-, and 1 : 4-axial groups. Such hindrance in the *O*-toluene-*p*-sulphonyl derivatives of 1 : 6-anhydro-β-D-altrose is considerable. In the change (VIII*a* ⟶ VIII*b*) the 3-hydroxyl group has to pass the 4-hydroxyl group, and the toluenesulphonyloxy-group will then show severe interaction with $O_{(1)}$ and $C_{(6)}$. 1 : 6-Anhydro-3 : 4-di-*O*-toluene-*p*-sulphonyl-β-D-altrose (XXIII) will also show a severe OTs/OTs interaction as the groups pass and, in the boat form, $OH_{(2)}/O_{(1)}$ and $OH_{(2)}/C_{(6)}$ interactions. It is considered that these factors are sufficient to prevent reaction under normal conditions. On the other hand, 1 : 6-anhydro-3-*O*-toluene-*p*-sulphonyl-β-D-altrose (XVII) does react and, although steric interaction is almost the same, the $OTs/OH_{(4)}$, $OH_{(2)}/O_{(1)}$, and $OH_{(2)}/C_{(6)}$ interactions could show the fine difference which distinguishes the compound from (VIII) and (XXIII).

This concept may be applied to methyl 4 : 6-*O*-benzylidene-2-*O*-toluene-*p*-sulphonyl-α(and β)-D-galactoside (XXVI). Although Reichstein and his co-workers found that both the α- and the β-form were converted into methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-D-taloside when boiled with sodium methoxide (*Helv. Chim. Acta*, 1945, **28**, 1, 226, 1164), Wiggins (*J.*, 1944, 522) observed that with cold sodium methoxide the β-form gave 78% of the anhydride after 15 min. while there was no reaction with the α-form. The chair conformation of the α-form is shown in (XXVI*a*) and it can be seen that there will be interactions on passing to (XXVI*b*) which will be similar to those in the 1 : 6-anhydro-β-D-altrose series. This example, however, is not so easy to interpret since the ring fusion at

$C_{(4)}/C_{(5)}$ is *cis* and this permits the pyranose ring to become 1 C in conformation (XXVI*c*). Even if this were so the β- and the α-anomer could still show different steric interactions to account for the behaviour which Wiggins observed.

Further consideration of steric interactions would suggest that methyl 4 : 6-*O*-benzylidene-2-*O*-toluene-*p*-sulphonyl-β-D-glucoside should react faster than the α-form which itself should react more slowly than the 3-toluene-*p*-sulphonate. Rate measurements, however, are required before these steric effects can be fully assessed.



Experimental

1 : 6-*Anhydro*-2-O-*toluene*-p-*sulphonyl*-β-D-*altrose*.—1 : 6-Anhydro-3 : 4-*O*-*iso*propylidene-2-*O*-toluene-*p*-sulphonyl-β-D-altrose (10 g.; Newth and Wiggins, *loc. cit.*) was boiled with 20% acetic acid (100 ml.) for 2 hr. On cooling, 1 : 6-*anhydro*-2-O-*toluene*-p-*sulphonyl*-β-D-*altrose* (8·5 g.) separated which, recrystallised from ethanol–water, had m. p. 129—130°, $[\alpha]_D^{17}$ −148·5° (*c*, 1·05 in EtOH) (Found: C, 49·4; H, 5·1. $C_{13}H_{16}O_7S$ requires C, 49·4; H, 5·1%). Acetylation (acetic anhydride–pyridine) yielded the 3 : 4-*di*-O-*acetate*, m. p. 139—140° (from ethanol), $[\alpha]_D^{20}$ −142·5° (*c*, 1·27 in $CHCl_3$) (Found: C, 51·0; H, 5·0. $C_{17}H_{20}O_9S$ requires C, 51·0; H, 5·0%).

1 : 6-*Anhydro* 2-O-*methanesulphonyl*-3 : 4-O-iso*propylidene*-β-D-*altrose*.—1 : 6-Anhydro-3 : 4-*O*-*iso*propylidene-β-D-altrose (2 g.) in pyridine (10 ml.) was treated with methanesulphonyl chloride (0·87 ml., 1·1 mol.) for 15 hr. The mixture was poured into water, and 1 : 6-*anhydro*-2-O-*methanesulphonyl*-3 : 4-O-iso*propylidene*-β-D-*altrose*, recrystallised from methanol, had m. p. 158—159° (1·7 g.), $[\alpha]_D^{22}$ −162° (*c*, 0·99 in $CHCl_3$) (Found: C, 43·2; H, 5·7. $C_{10}H_{16}O_7S$ requires C, 42·9; H, 5·7%).

1 : 6-*Anhydro*-2-O-*methanesulphonyl*-β-D-*altrose*.—The *iso*propylidene derivative (1·7 g.) was boiled in ethanol (60 ml.) and 0·5N-sulphuric acid (30 ml.) for 2 hr. The acid was neutralised with barium hydroxide and, after removal and washing of the inorganic precipitate, the solution was evaporated to dryness. The residue, recrystallised from ethanol, afforded 1 : 6-*anhydro*-2-O-*methanesulphonyl*-β-D-*altrose* (1·3 g.), m. p. 138—140°, $[\alpha]_D^{22}$ −186·4° (*c*, 0·77 in EtOH) (Found: C, 35·1; H, 5·2. $C_7H_{12}O_7S$ requires C, 35·0; H, 5·0%). The 3 : 4-*di*-O-*acetate*, recrystallised from ethanol, had m. p. 139°, $[\alpha]_D^{18}$ −157·5° (*c*, 0·95 in $CHCl_3$) (Found: C, 40·6; H, 5·0. $C_{11}H_{16}O_9S$ requires C, 40·7; H, 4·9%).

Attempted Formation of 1 : 6-2 : 3-*Dianhydro*-β-D-*allose*.—1 : 6-Anhydro-2-*O*-toluene-*p*-sulphonyl-β-D-altrose and 1 : 6-anhydro-2-*O*-methanesulphonyl-β-D-altrose were recovered unchanged after they had been treated with boiling 0·5N-sodium methoxide solution (1 equiv.) for 5 hr. or N-sodium hydroxide (1 equiv.) at 95° for 6 hr. 1 : 6-Anhydro-2-*O*-toluene-*p*-sulphonyl-β-D-altrose was also recovered unchanged after treatment in boiling butan-1-ol with a solution from sodium (1 atom equiv.) in butan-1-ol. When this compound was heated with a solution of sodium methoxide (3 equiv.) at 120° for 22 hr. and the resulting dark brown solution neutralised, a highly coloured resin was obtained which could not be characterised. 3 : 4-Di-*O*-acetyl-1 : 6-anhydro-2-*O*-toluene-*p*-sulphonyl- and -2-*O*-methanesulphonyl-β-D-altrose were deacetylated quantitatively when their chloroform solutions were treated with sodium methoxide (3 equiv.) in methanol for 16 hr. 1 : 6-Anhydro-2-chloro-2-deoxy-β-D-altrose was recovered after its treatment with 0·5N-sodium hydroxide (1 equiv.) at 18° for 20 hr.

1 : 6-*Anhydro*-2-O-*benzoyl*-3 : 4-O-iso*propylidene*-β-D-*altrose*.—1 : 6-Anhydro-3 : 4-*O*-*iso*propylidene-β-D-altrose (6·45 g.) in pyridine (50 ml.) was treated with benzoyl chloride (4·9 g., 1·1 mol.). The mixture was poured into water after 15 hr. and the precipitate removed and washed with water. 1 : 6-*Anhydro*-2-O-*benzoyl*-3 : 4-O-iso*propylidene*-β-D-*altrose* (7·3 g.), recrystallised from

ethanol, had m. p. 95—96°, $[\alpha]_D^{20}$ −212·6° (*c*, 1·17 in $CHCl_3$) (Found : C, 62·7; H, 5·9. $C_{15}H_{16}O_6$ requires C, 62·7; H, 5·8%).

1 : 6-*Anhydro*-2-O-*benzoyl*-β-D-*altrose*.—The 3 : 4-*O*-*iso*propylidene derivative (4·5 g.) was boiled with 20% acetic acid (100 ml.) for 2 hr. The solution was evaporated and 1 : 6-*anhydro*-2-O-*benzoyl*-β-D-*altrose* (3·9 g.) separated which, recrystallised from ethanol, had m. p. 203—204°, $[\alpha]_D^{20}$ −220·5° (*c*, 0·84 in $COMe_2$) (Found : C, 58·6; H, 5·3. $C_{13}H_{14}O_6$ requires C, 58·6; H, 5·3%). The 3 : 4-*di*-O-*acetate* had m. p. 117—118° (from ethanol), $[\alpha]_D^{18}$ −203° (*c*, 2·98 in $CHCl_3$) (Found : C, 58·3; H, 5·3. $C_{17}H_{18}O_8$ requires C, 58·3; H, 5·1%).

1 : 6-*Anhydro*-2-O-*benzoyl*-3 : 4-*di*-O-*toluene*-p-*sulphonyl*-β-D-*altrose*.—1 : 6-Anhydro-2-*O*-benzoyl-β-D-altrose (3·0 g.) in pyridine (30 ml.) was treated with toluene-*p*-sulphonyl chloride (4·75 g., 2·2 mol.) for 20 hr. When the mixture was then poured into water, 1 : 6-*anhydro*-2-O-*benzoyl*-3 : 4-*di*-O-*toluene*-p-*sulphonyl*-β-D-*altrose* separated which, recrystallised from ethanol (4·4 g., 70%), had m. p. 187—188°, $[\alpha]_D^{20}$ −214° (*c*, 0·92 in $CHCl_3$) (Found : C, 56·3; H, 4·4; S, 11·4. $C_{27}H_{26}O_{10}S_2$ requires C, 56·4; H, 4·5; S, 11·2%). The residue from the mother-liquors, recrystallised from ethanol, had m. p. 176—177° (0·8 g.), $[\alpha]_D^{18}$ −238° (*c*, 2·22 in $CHCl_3$), and was 1 : 6-*anhydro*-2-O-*benzoyl*-3-O-*toluene*-p-*sulphonyl*-β-D-*altrose* (Found : C, 57·2; H, 5·1; S, 7·7. $C_{20}H_{20}O_6S$ requires C, 57·2; H, 5·1; S, 7·6%). This derivative was obtained quantitatively when 1 : 6-anhydro-2-*O*-benzoyl-β-D-altrose (166 mg.) was treated with toluene-*p*-sulphonyl chloride (118 mg.) in pyridine at 0° for 48 hr. Benzoylation of 1 : 6-anhydro-2-*O*-benzoyl-3-*O*-toluene-*p*-sulphonyl-β-D-altrose gave the 2 : 4-*di*-O-*benzoate*, m. p. 125° (from ethanol), $[\alpha]_D^{18}$ −215° (*c*, 0·92 in $CHCl_3$) (Found : C, 61·9; H, 4·7. $C_{27}H_{24}O_9S$ requires C, 61·8; H, 4·6%).

1 : 6-*Anhydro*-3-O-*toluene*-p-*sulphonyl*-β-D-*altrose*.—1 : 6-Anhydro-2-*O*-benzoyl-3-*O*-toluene-*p*-sulphonyl-β-D-altrose (0·56 g.) in chloroform (5 ml.) was treated with a solution from sodium methoxide (from 70 mg. of sodium ; 2·2 mol.) in methanol (5 ml.). Excess of alkali was neutralised with carbon dioxide after 16 hr. and the solution evaporated. The dry residue was extracted with acetone and the crystalline residue from this extract was 1 : 6-*anhydro*-3-O-*toluene*-p-*sulphonyl*-β-D-*altrose* (185 mg.), m. p. 144—145° (from acetone–ether), $[\alpha]_D^{21}$ −168·5° (*c*, 1·18 in MeOH) (Found : C, 49·2; H, 4·9. $C_{13}H_{16}O_7S$ requires C, 49·4; H, 5·0%). It was not oxidised by aqueous sodium metaperiodate.

Treatment of 1 : 6-*Anhydro*-3-O-*toluene*-p-*sulphonyl*-β-D-*altrose with Sodium Methoxide*.—The compound (750 mg.) was boiled for 2 hr. in a solution of methanol (20 ml.) containing sodium (140 mg., 2·5 mol.). The dark mixture was neutralised with carbon dioxide and then evaporated and the residue extracted with ethyl acetate. The crystalline *dianhydride* (70 mg.) obtained from this extract, recrystallised from ethyl acetate, had m. p. 158°, $[\alpha]_D^{20}$ −108° (*c*, 0·75 in $COMe_2$) (Found : C, 50·2; H, 5·7. $C_6H_8O_4$ requires C, 50·0; H, 5·6%). 1 : 6-Anhydro-3-*O*-toluene-*p*-sulphonyl-β-D-altrose was unaffected by the above treatment with only 1 atom equiv. of sodium.

The dianhydride was identified as 1 : 6-3 : 4-*dianhydro*-β-D-*altrose* by acidic hydrolysis (2·8 mg. in 0·2 ml. of 0·1N-sulphuric acid at 80° for 2 hr.). Paper chromatography of the product (pyridine–ethyl acetate–water, 1 : 2 : 2, top layer) showed it to be 1 : 6-anhydro-β-D-glucose or -mannose [lead tetra-acetate spray reagent (Buchanan, Dekker, and Long, *J.*, 1950, 3162)]. Paper ionophoresis (0·1M-sodium tetraborate, 200 v for 5 hr.) distinguished the product as 1 : 6-anhydro-β-D-mannose. Authentic specimens of 1 : 6-anhydro-β-D-altrose, -β-D-glucose, -β-D-idose, and -β-D-mannose were used as markers.

1 : 6-*Anhydro*-3 : 4-*di*-O-*toluene*-p-*sulphonyl*-β-D-*altrose*.—To a solution of 1 : 6-anhydro-2-*O*-benzoyl-3 : 4-di-*O*-toluene-*p*-sulphonyl-β-D-altrose (4·4 g.) in chloroform (50 ml.), sodium methoxide (from 0·4 g. of sodium) in methanol (25 ml.) was added at 0°. Within 15 min. the sparingly soluble product which had separated was removed and washed with water. To this was added a further small amount obtained on evaporating the chloroform layer. 1 : 6-*Anhydro*-3 : 4-*di*-O-*toluene*-p-*sulphonyl*-β-D-*altrose*, recrystallised from ethanol, had m. p. 209°, $[\alpha]_D^{20}$ −147° (*c*, 0·73 in $CHCl_3$) (Found : C, 51·1; H, 4·7. $C_{20}H_{22}O_8S$ requires C, 51·1; H, 4·7%). The compound was unaffected by boiling 2·5M-sodium methoxide for 20 hr.

This work was carried out during the tenure of an I.C.I. Fellowship. The author gratefully acknowledges a generous gift of 1 : 6-anhydro-β-D-altrose monohydrate and specimens of 1 : 6-anhydro-β-D-mannose and tri-*O*-acetyl-1 : 6-anhydro-β-D-idose from Dr. Nelson K. Richtmyer, National Institutes of Health, Bethesda, Md.

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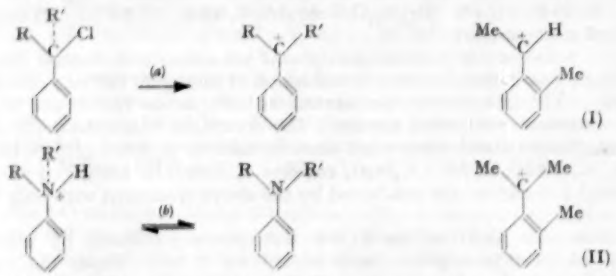
88. *Steric Relations between Ionisation of Aralkyl Chlorides and Dissociation of Anilinium Ions. Part II.**

By G. Baddeley, J. Chadwick, and H. T. Taylor.

Rates of ethanolysis of several tertiary aralkyl chlorides RR'CAr·Cl have been determined and compared with the dissociation constants of the corresponding anilinium ions $RR'NArH^+$. The comparison supports the view [1] that ionisation of the chlorides and dissociation of the anilinium ions effect changes of intramolecular conformation which increase intramolecular steric interaction.

Ionisation process (*a*) and dissociation (*b*) (see formulæ) incur similar changes in intramolecular conformation and, therefore, are probably affected by similar changes in steric interaction: aralkyl chloride and anilinium ion, being comparatively free from mesomeric phenomena, will prefer those conformations in which R and R', should these be bulky groups, avoid the plane of the benzene ring whereas these groups must be in or near this plane in the benzyl cation and in the amine if these are to have maximum resonance energy. Thus both reactions are expected to be hindered by the increase in steric interaction as R and R' approach the plane of the ring and by loss of resonance energy in the benzyl cation and in the amine if these, for steric reasons, are not approximately planar. Consequently, in a series of chlorides and amines in which the members differ mainly in the magnitude of this steric effect, the more basic amines will be those corresponding to the less reactive chlorides and *vice versa*. In Part I secondary aralkyl chlorides R·CHArCl and the corresponding secondary amines R·NHAr were shown to be so related. This relation, which is



the opposite of that which usually obtains in the absence of this steric effect, is now shown to obtain between tertiary aralkyl chlorides RR'CArCl (R and R' = alkyl) and the corresponding tertiary amines RR'NAr.

Rates of ethanolysis of the chlorides in absolute ethanol were determined at two temperatures; the results are assembled in Table 1 and show that, in general, increased

Table 1. *Constants of Arrhenius equation, $k = Ae^{-E/RT}$, for the formation of hydrogen chloride by the ethanolysis of the chlorides.*

	$10^7 k_{0.0}$ (sec.$^{-1}$)	$10^5 k_{35.0}$ (sec.$^{-1}$)	E (kcal./mole)	$10^{-13}A$ (sec.$^{-1}$)
Ph·CMe$_2$Cl	147	34·7	21·4	1·5
Ph·CMeEtCl	34·2	9·72	22·8	4·7
Ph·CEt$_2$Cl	2·82	1·15	25·3	35·5
Ph·CPr$_2$Cl	9·58	3·48	24·5	28·2
Ph·CBu$_2$Cl	11·4	3·98	24·2	13·6
o-C$_6$H$_4$Me·CMe$_2$Cl ...	512	127	21·9	13·2
o-C$_6$H$_4$Me·CEt$_2$Cl	24·3	9·15	24·7	115

reactivity is caused by diminution in activation energy (E) and that the action constant (A) varies so as to compensate partly for the change in E.

* Part I, *J.*, 1954, 2405.

[1] Baddeley, Chadwick, and Taylor, *J.*, 1954, 2405.

The most noticeable feature is the *decrease* in reactivity as each methyl group of 2-chloro-2-phenylpropane is replaced by ethyl. It is not caused by change in inductive, inductomeric, or hyperconjugative effect since, as illustrated by comparison of the first and the third set of data in Table 4, the same change of alkyl group in tertiary alkyl chlorides provides a small *increase* in the rate of unimolecular solvolysis. Consideration of the change of intramolecular steric interaction which affects ionisation of the aralkyl chlorides provides an explanation: in these chlorides, steric interaction of alkyl groups and the benzene ring orients the former at a distance from the plane of the latter and ionisation is therefore energetically hindered by the increase in steric interaction as the alkyl groups move towards the plane of the ring to provide maximum resonance stabilisation of the resulting carbonium ion. Differences (i), (ii), and (iii) of Table 2 show that replacement of a methyl by an ethyl group (Ph·CRMeCl ⟶ Ph·CREtCl) increases the energy of activation of ionisation by an amount which is small (0·3 kcal./mole) when R = H and increases to 1·4 and 2·5 kcal./mole when R is Me and Et respectively. These increments indicate that repulsive forces between R and the neighbouring ethyl group tend to orient the latter with its terminal methyl group close to the benzene ring and that this effect increases in the order R = H < Me < Et. This "buttressing-effect" has been discerned previously in the dissociation constants and heats of formation (ΔH) of addition compounds of aliphatic amines with trimethylboron:[2] $RR'R''N + BMe_3 \rightleftharpoons RR'R''\overset{+}{N}\cdot\overset{-}{B}Me_3$; compare differences (i) and (v), and (iv) and (vi), of Table 2. Whereas the steric effects of methyl and ethyl groups are very similar in the addition compounds obtained from methyl- and ethyl-amine severally, they are very different in those from dimethyl- and diethyl-amine. In the latter, each ethyl group is "buttressed" by the other and thus their terminal methyl groups are pressed closer to the trimethylboron moiety.

TABLE 2.

	E		E		E
(i) Ph·CHEtCl	20·7	(ii) Ph·CMeEtCl	22·8	(iii) Ph·CEtEtCl	25·3
Ph·CHMeCl	20·4	Ph·CMeMeCl	21·4	Ph·CEtMeCl	22·8
	0·3		1·4		2·5
	E		ΔH		ΔH
(iv) Ph·CEt$_2$Cl	25·3	(v) $Me_3\overset{-}{B}\cdot\overset{+}{N}H_2Et$	−18·00	(vi) $Me_3\overset{-}{B}\cdot\overset{+}{N}HEt_2$	−16·31
Ph·CMe$_2$Cl	21·4	$Me_3\overset{-}{B}\cdot\overset{+}{N}H_2Me$	−17·62	$Me_3\overset{-}{B}\cdot\overset{+}{N}HMe_2$ ...	−19·26
	3·9		− 0·38		2·95

Whereas the energies of activation for solvolysis of Ph·CMe$_2$Cl and Ph·CEt$_2$Cl differ by 3·9 kcal./mole, those for *o*-C$_6$H$_4$Me·CMe$_2$Cl and *o*-C$_6$H$_4$Me·CEt$_2$Cl differ by only 2·8. This partial neutralisation of the difference between the steric effects of methyl and ethyl groups by the *o*-methyl group is probably caused by this group's giving added importance to the steric effect of that part of the side-chain alkyl group which is directly attached to the seat of reaction.

The above arguments in which difference between the effect of methyl and ethyl groups on the reactivity of aralkyl chlorides is attributed to steric causes is supported by comparison of the logarithms of the velocity constants for solvolysis of the chlorides Ar·CRR'Cl with the values of pK_a for the structurally related amines Ar·NRR' (see Table 4, first and second sets). It shows, what must be expected from steric considerations, that the most basic amines are those which correspond to the least reactive chlorides and *vice versa*. An obvious exception arises on introduction of an *o*-methyl group since this affords chlorides and amines of comparatively high reactivity and basic strength respectively. Thus, as must be expected, the *o*-methyl group exerts an electronic as well as a steric effect. The latter is revealed by (*a*) the fact that *o*-C$_6$H$_4$Me·CMe$_2$Cl is *more* reactive than *o*-C$_6$H$_4$Me·CEt$_2$Cl whereas *o*-C$_6$H$_4$Me·NMe$_2$ is *less* basic than *o*-C$_6$H$_4$Me·NEt$_2$, and

[2] Brown *et al.*, *J. Amer. Chem. Soc.*, 1944, **66**, 435; 1947, **69**, 1332; 1951, **73**, 2464.

(*b*) the data assembled in Table 3. They show that introduction of an *o*-methyl group into 1-phenylethyl chloride gives a 34-fold increase in rate and a diminution of 2·8 kcal./mole in the energy of activation (consequences of the inductive and hyperconjugative effects of the methyl group), whereas introduction of *o*-methyl group into 2-chloro-2-phenylpropane affords little more than a 3-fold increase in rate and no diminution in the energy of activation. In this instance the electronic effects of the methyl group are essentially neutralised by a comparatively large steric effect [cf. (I) and (II)].

TABLE 3.

	$10^5k_{0\cdot0}$ (sec.$^{-1}$)	*E* (kcal./mole)		$10^7k_{0\cdot0}$ (sec.$^{-1}$)	*E* (kcal./mole)
o-$C_6H_4Me{\cdot}CHMeCl$ ...	110	22·8	*o*-$C_6H_4Me{\cdot}CMe_2Cl$	512	21·9
$Ph{\cdot}CHMeCl$	3·23	25·6	$Ph{\cdot}CMe_2Cl$	147	21·4

TABLE 4.

	log $k_{0\cdot0}$	Ref. *a*	pK_a	Ref. *b*	log $k_{25\cdot0}$	Ref. *c*	pK_a
$Ph{\cdot}CMe_2Cl$	2·17	$Ph{\cdot}NMe_2$	5·06	$Me{\cdot}CMe_2Cl$	2·17	$H{\cdot}NMe_2$ ...	10·71
$Ph{\cdot}CMeEtCl$	1·53	$Ph{\cdot}NMeEt$	5·98	$Me{\cdot}CMeEtCl$ ...	2·40	$H{\cdot}NMeEt$ ...	—
$Ph{\cdot}CEt_2Cl$	0·45	$Ph{\cdot}NEt_2$	6·56	$Me{\cdot}CEt_2Cl$	2·60	$H{\cdot}NEt_2$ ...	10·98
$Ph{\cdot}CPrCl$	0·98	$Ph{\cdot}NPr_2$	5·59				
$Ph{\cdot}CBu_2Cl$	1·06	$Ph{\cdot}NBu_2$	5·7				
o-$C_6H_4Me{\cdot}CMe_2Cl$ ...	2·71	*o*-$C_6H_4Me{\cdot}NMe_2$ ...	5·86				
o-$C_6H_4Me{\cdot}CEt_2Cl$ ...	1·39	*o*-$C_6H_4Me{\cdot}NEt_2$ ...	7·18				

[a] In aqueous solution: Vexlearschi and Rumpf, *Compt. rend.*, 1949, **229**, 1152. [b] In 80% aqueous ethanol: Hughes, *Quart. Rev.*, 1951, **5**, 257. [c] In aqueous solution: Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1930, **52**, 5115; 1932, **54**, 3469.

Further lengthening of the alkyl group to include *n*-propyl and *n*-butyl groups (see Tables 1 and 4) seems to afford steric effects which are smaller than that of the ethyl group: the resulting chlorides have comparatively high reactivity and the corresponding amines have comparatively low basic strength.

EXPERIMENTAL

Materials.—Chlorides. Dry hydrogen chloride was passed for 3 hr. though an ice-cold solution of 2-phenylpropan-2-ol (5 g.) in light petroleum (25 c.c.). An aqueous layer separated; the organic layer was decanted and dried ($CaCl_2$), and the solvent was volatilised at 25—30° under reduced pressure. The residue was mainly 2-phenyl-2-chloropropane (Found: Cl, 22·6. Calc. for $C_9H_{11}Cl$: 23·0%). The other tertiary aralkyl chlorides were similarly obtained and contained 94—98% of the calculated amount of chlorine. The required dialkylphenylmethanols RR'CPh·OH were obtained as previously described.[3] 2-*o*-Tolylpropan-2-ol, m. p. 43°, was obtained in the manner described by Hirschberg,[4] and 3-*o-tolylpentan*-3-*ol*, b. p. 125—126°/22 mm. (Found: C, 80·8; H, 10·1. $C_{12}H_{18}O$ requires C, 80·9; H, 10·1%), was similarly obtained by reaction of *o*-tolylmagnesium bromide with diethyl ketone.

Solvent.—One batch of ethanol which had been purified by the process described by Lund and Bjerrum [5] was used throughout.

Determination of Rates of Solvolysis of the Chlorides.—This was effected by the sampling method described by Hughes, Ingold, and Taher.[6] Freshly prepared samples of the chlorides were used immediately after removal of the solvent in which they had been prepared. Distillation of the chlorides under reduced pressure gave distillates which contained much less halogen than was required. Before and after distillation the chlorides provided rates of ethanolysis which did not differ by more than the experimental error (*ca.* 3%). Duplicate determinations were made in every case.

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[3] Klages, *Ber.*, 1902, **35**, 2637, 3507; 1903, **36**, 3692; Gilman and Adams, *J. Amer. Chem. Soc.*, 1925, **47**, 2818; Gilman, Fothergill, and Parker, *Rec. Trav. chim.*, 1929, **48**, 750.
[4] Hirschberg, *J. Amer. Chem. Soc.*, 1949, **71**, 3241.
[5] Lund and Bjerrum, *Ber.*, 1931, **64**, 210.
[6] Hughes, Ingold, and Taher, *J.*, 1940, 949.

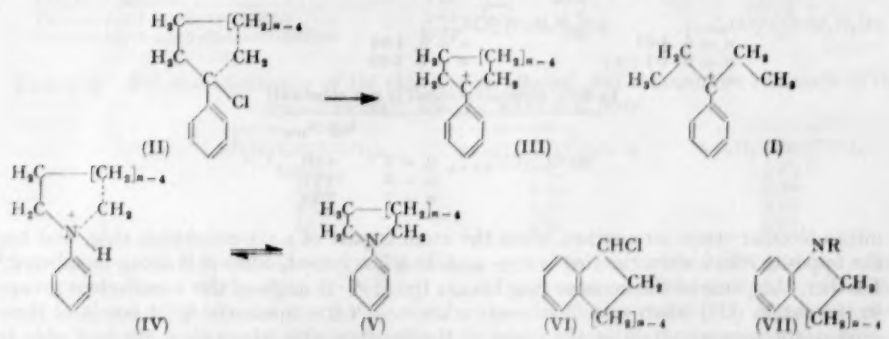
89. *Steric Relations between Ionisation of Aralkyl Chlorides and Dissociation of Anilinium Ions. Part III.**

By G. Baddeley, J. Chadwick, and H. T. Taylor.

Rates of solvolysis of the chlorides $C_6H_5{\cdot}\overline{CCl{\cdot}[CH_2]_{n-1}}$ and their *o*-methyl derivatives in absolute ethanol, where *n* is 5, 6, and 7 severally, and the basic strengths of the corresponding amines $C_6H_5{\cdot}\overline{N{\cdot}[CH_2]_{n-1}}$ and their *o*-methyl derivatives in 50% aqueous ethanol have been measured. Reactivity of the chlorides *decreases* in the order $n = 5 > 7 > 6$ and, since this is the order of *increasing* basic strength of the amines, it is argued that this is the order of increasing steric hindrance of ionisation of the chlorides and of dissociation of the anilinium ions.

Reactivity of the chlorides $o\text{-}\overline{C_6H_4{\cdot}CHCl{\cdot}[CH_2]_{n-3}}$ *decreases* in the order $n = 5 > 6 > 7$, and our belief [1] that this is the order of increasing steric hindrance of ionisation of the chlorides is now further substantiated by the fact that this is the order of increasing basic strength of the corresponding amines $o\text{-}\overline{C_6H_4{\cdot}NH{\cdot}[CH_2]_{n-3}}$ and of their *N*-methyl derivatives.

In Part II,[2] ionisation of the chloride $Ph{\cdot}CR_2Cl$ and dissociation of the corresponding anilinium ion $Ph{\cdot}NR_2H^+$ were shown to be more hindered when R is ethyl than when it is a methyl group, and it was suggested that the ethyl group exerts the greater steric effect as a consequence of intramolecular steric interaction of its terminal methyl group and the benzene ring in the benzyl cation (I) and in the free amine $Ph{\cdot}NEt_2$. If this were so, then enclosure of the ethyl groups in a ring system, as in 1-phenyl*cyclo*pentyl chloride (II; $n = 5$) and 1-phenylpyrrolidine (V; $n = 5$) and the corresponding six- and seven-membered



ring systems (II and V; $n = 6$ and 7), should obviate this effect. The data assembled in Table 2, sets 1 and 2, show that it does: 3-phenyl-3-chloropentane ($Ph{\cdot}CEt_2Cl$) is the least reactive chloride while *N*-diethylaniline has the greatest basic strength.

Rates of ethanolysis of the 1-phenyl*cyclo*alkyl chlorides (II; $n = 5$, 6, and 7) and the *o*-methyl derivatives of the first two are given in Table 1; those of 2-phenyl-2-chloropropane and 3-phenyl-3-chloropentane are included for comparison; in general, increased reactivity is caused largely by diminution in activation energy (E).

The order of reactivity (II; $n = 5 > 7 > 6$) is probably caused by two mutually supporting steric effects. One arises from steric interaction of the aromatic and the alicyclic moieties: the five-membered ring of 1-phenyl*cyclo*pentyl cation (III; $n = 5$)

* Part II, preceding paper.
[1] Baddeley and Chadwick, *J.*, 1951, 368.
[2] Baddeley, Chadwick, and Taylor, preceding paper.

withdraws the α-methylene groups from the *ortho*-positions of the benzene ring and consequently the change of conformation which accompanies ionisation of the chloride (II) (the α-methylene groups are brought into the plane of the benzene ring) provides a smaller increase in steric interaction when n is 5 than when it is 6 or 7. The other steric effect is provided by change in conformation of the alicyclic moiety during the ionisation process: change in co-ordination number of a ring-carbon atom from four to three, as in (II ⟶ III), increases the number and degree of unfavourable conformations, *i.e.*, increases

TABLE 1. *Constants of the Arrhenius equation, $k = Ae^{-E/RT}$, for the formation of hydrogen chloride by ethanolysis of the chlorides.*

		$10^5 k_{0\cdot0}$ (sec.$^{-1}$)	$10^5 k_{25\cdot0}$ (sec.$^{-1}$)	E (kcal./mole)	$10^{-11}A$ (sec.$^{-1}$)
Ph·CMe$_2$Cl		1·47	34·7	21·4	15
Ph·CEt$_2$Cl		0·0282	1·15	25·3	47
Ph·CCl·[CH$_2$]$_{n-1}$	$n = 5$	108	1445 [a]	17·3	0·37
	$n = 6$	0·160	5·90	23·5	76
	$n = 7$	30·2	724 [b]	20·8	105
o-C$_6$H$_4$Me·CCl·[CH$_2$]$_{n-1}$	$n = 5$	470	—		
	$n = 6$	(1·27—0·89)	(40—24)		

[a] By calculation, using $10^5 k_{10\cdot0} = 325$ sec.$^{-1}$. [b] By calculation, using $10^5 k_{10\cdot0} = 116$ sec.$^{-1}$.

TABLE 2.

In ethanol

(1)		log $10^7 k_{0\cdot0}$
Ph·CMe$_2$Cl		2·17
Ph·CEt$_2$Cl		0·45
Ph·CCl·[CH$_2$]$_{n-1}$	$n = 5$	4·63
	$n = 6$	1·20
	$n = 7$	3·48
o-C$_6$H$_4$Me·CCl·[CH$_2$]$_{n-1}$	$n = 5$	4·67
	$n = 6$	2·1 (*ca.*)

In 50% aqueous ethanol at 20°

(2)		pK_a
Ph·NMe$_2$		4·22
Ph·NEt$_2$		5·71
Ph·N·[CH$_2$]$_{n-1}$	$n = 5$	3·71
	$n = 6$	4·60
	$n = 7$	—
o-C$_6$H$_4$Me·N·[CH$_2$]$_{n-1}$	$n = 5$	4·88
	$n = 6$	5·20

(3)		pK_a
HN·[CH$_2$]$_{n-1}$	$n = 5$	10·37
	$n = 6$	10·14
	$n = 7$	10·30

(4)		pK_a
MeN·[CH$_2$]$_{n-1}$	$n = 5$	9·82
	$n = 6$	9·24
	$n = 7$	9·68

In 80% aqueous ethanol (c is a constant)

(5)		log $ck_{25\cdot0}$
Me·CCl·[CH$_2$]$_{n-1}$	$n = 5$	4·00
	$n = 6$	1·91
	$n = 7$	3·88

intramolecular steric interaction, when the atom is part of a six-membered ring, and has the opposite effect when the ring is five- and, to a less extent, when it is seven-membered.[3] Further, the plane of the benzene ring bisects the H–C–H angle of the α-methylene groups in the cation (III) when $n = 5$, whereas when $n = 6$ the equatorial C–H bonds of these groups are approximately in the plane of the benzene ring where they are best able to provide steric interaction. Similar, though in part smaller, changes in number and degree of unfavourable conformations affect ionisation of 1-methyl*cyclo*alkyl chlorides, and the rates of solvolysis of the 1-phenyl- and 1-methyl-*cyclo*alkyl chlorides (Table 2, sets 1 and 5 respectively) reveal this similarity.

Dissociation of the conjugate acids of the amines listed in sets 3 and 4 of Table 2, unlike the ionisation of the chlorides of set 5, effects little change of conformation (the tetrahedral sp^3 distribution of the electrons of the nitrogen atom is common to the amines and their conjugate acids) and there is no cause for the basic strengths of these amines to vary inversely as the reactivities of the chlorides of set 5. In fact, d log k/d pK_a is positive and thereby affords evidence for an electronic effect whereby accession of electrons to the seat of reaction is greater in the five- than in the seven- and six-membered rings.

On the other hand, dissociation of the conjugate acids of the *N*-phenylamines of Table

[3] H. C. Brown and Borkowski, *J. Amer. Chem. Soc.*, 1952, **74**, 1894; *Ann. Reports*, 1954, **51**, 170.

2, set 2, is expected to involve conformational changes resembling those effected by ionisation of the 1-phenyl*cyclo*alkyl chlorides of set 1: (*a*) The conjugate acids (IV), being comparatively free from mesomeric phenomena, will prefer those conformations in which the α-methylene groups avoid the plane of the benzene ring whereas these groups must lie near this plane in the amines if these are to enjoy maximum resonance stabilisation. (*b*) The nitrogen atoms of the conjugate acids have a tetrahedral distribution of bonds whereas the free amino-groups are considerably "flattened" by conjugation of nitrogen atom and phenyl group. The resemblance between the conformational changes involved in the two processes, dissociation and ionisation, results in 1-phenylpyrrolidine's having a smaller basic strength than has 1-phenylpiperidine while 1-phenyl*cyclo*pentyl chloride is more reactive than 1-phenyl*cyclo*hexyl chloride.

The 1-*o*-tolyl*cyclo*alkyl chlorides are more reactive than the corresponding 1-phenyl derivatives; the steric effect of the *o*-methyl group is apparently more than neutralised by electronic effects. The negative value of d ln k/d pK_a is evidence for steric hindrance in the reactions of the *o*-tolyl derivatives.

Similarity of conformational change also relates dissociation of the conjugate acids of the benzocyclamines (VII; R = H and Me) and ionisation of the chlorides (VI) where n is 5, 6, and 7 severally. The relevant data are listed in Table 3; those for the chlorides have previously been reported [1] and those for the bases are now provided. d ln k/d pK_a is negative and thereby indicates that both processes are sterically hindered by the conformational changes they incur when $n = 7$ and, to smaller extent, when $n = 6$; such hindrance is absent when $n = 5$ since little change in conformation is then involved.

Knowing the basic strengths of the benzocyclamines we are able to comment on the relative rates of hydrogen exchange between these bases and acidic reagent (see Table 4).

TABLE 3.

	pK_a	Relative [D$^+$]	Hydrogen exchange no.
Dimethylaniline	4·22	6·0	0·12
1-Methylindoline	3·69	20·4	1·58
Tetrahydro-1-methylquinoline	3·86	13·8	0·87
Tetrahydro-1-methylhomoquinoline	4·44	3·6	0·00

TABLE 4. *Relative reactivities of the chlorides in ethanol, and dissociation constants of the amines in* 50% *aqueous ethanol at* 20·0°.

	o-C_6H_4·CHCl·[CH_2]$_{n-3}$	*o*-C_6H_4·NH·[CH_2]$_{n-3}$	*o*-C_6H_4·NMe·[CH_2]$_{n-3}$
n	log $ch_{0\cdot0}$	pK_a	pK_a
5	4·20	4·23	3·69
6	3·63	4·41	3·86
7	1·97	4·82	4·44

The rates, given [4] by d[D]/dt = k[D$^+$][Amine], decrease in the order $n = 5 > 6 \gg 7$, and W. G. Brown, Widiger, and Letang,[5] assuming that the values of k decrease correspondingly, explained the falls in rate in terms of steric hindrance of conjugation in the transition state; their explanation would be acceptable if the concentrations of the reactants were independent of the value of n, *i.e.*, if the basic strengths of these cyclamines were equal; they are not. Excess of the cyclamines was used and, as a consequence of the effect of the value of n on the magnitude of the conformational changes accompanying dissociation of the conjugate acids of (VII), the relative concentrations (or activities) of acid decreased in the order $n = 5 > 6 > 7$ and, at least in part, were the cause of the differences in the rates of exchange.

Our interpretation of the effect of ring size on the properties of these cyclamines and the analogous cyclic ketones (VII; >CO in place of >NR) was given in a letter [6] and in a paper: [1] Heddon and W. G. Brown,[7] referring only to the letter, say "Nor do they explain why their interpretation of the amine spectra, based upon the steric requirements for

[4] Ingold, Raisin, and Wilson, *J.*, 1936, 1637; Best and Wilson, *J.*, 1938, 28.
[5] W. G. Brown, Widinger, and Letang, *J. Amer. Chem. Soc.*, 1939, **61**, 2597.
[6] Baddeley, Chadwick, and Rawlinson, *Nature*, 1949, **164**, 833.
[7] Heddon and W. G. Brown, *J. Amer. Chem. Soc.*, 1953, **75**, 3744.

hyperconjugation, should not apply equally to the analogous cyclic ketones" and, discussing the absorption spectra of the cyclic ketones, "it appears unnecessary to invoke hyperconjugation, and its dependence upon the orientation of the methylene groups, as these authors have done;" and "Nor is the present series a suitable one for the demonstration of such minor effects since, by varyimg the ring size, the orientation of the ortho methylene groups cannot be altered without also affecting the orientation of the carbonyl group." It is clear that they believe that we consider the effect of ring size on conjugation in these systems to be determined in some unspecified way by hyperconjugation; we wish to place it on record that their belief is mistaken. Further, in the last paragraph of their discussion they write: "the B-band intensities for $n = 2$ and 3 are substantially higher than, and at $n = 4$ approximately equal to, the intensity of the corresponding transition in acetophenone. This situation is perhaps the basis for the statement of Baddeley, Chadwick and Rawlinson to the effect that it is the compounds with five- and six-membered rings, not the seven-, that are abnormal." Their surmise is wrong, as our letter [6] and our paper [1] in the *Journal* show.

Experimental

Materials.—Chlorides. When 1-phenyl*cyclo*hexyl and 1-phenyl*cyclo*heptyl chloride were obtained from the corresponding alcohols in solution in light petroleum (5 g. in 25 c.c.) by passing in dry hydrogen chloride for 3 hr., their solvolyses gave velocity coefficients which decreased as reaction proceeded; the chlorides were obviously impure and preparation had apparently involved partial isomerisation. This difficulty was overcome by passing hydrogen chloride into *dilute* solutions (5 g. in 500 c.c.) of the alcohols in light petroleum and by having present finely powdered anhydrous calcium chloride (10 g.). The structures of the chlorides were established by hydrolysis and identification of the resulting alcohols. Similar attempts to obtain pure 1-*o*-tolyl*cyclo*hexyl chloride from the corresponding *cyclo*hexanol or from 1-*o*-tyl*cyclo*hexene failed. The 1-*o*-tolyl*cyclo*hexyl cation, if only as part of an ion pair, is a likely intermediate in the preparation of the chloride, and ready isomeration of the cation can reasonably be attributed to steric hindrance of conjugation and consequent loss of resonance stabilisation.

1-Phenyl- and 1-*o*-tolyl-*cyclo*pentyl chloride were prepared by passing dry hydrogen chloride through 1-phenyl- and 1-*o*-tolyl-*cyclo*pentene at 0° and subsequently removing hydrogen chloride by a stream of dry nitrogen; they contained only 80—90% of the calculated amount of chlorine. 1-*Phenyl*cyclo*hexyl chloride* was prepared from 1-phenyl*cyclo*hexanol: dry hydrogen chloride was passed for 3 hr. through a mixture of this alcohol (5 g.), anhydrous calcium chloride (10 g.), and light petroleum (500 c.c.). The mixture was filtered and calcium chloride was added to the filtrate. After an hour the calcium chloride was separated by filtration and the solvent by evaporation under reduced pressure. The residue contained Cl, 18·2% ($C_{12}H_{15}Cl$ requires Cl, 18·5%). 1-*o*-Tolyl*cyclo*hexyl chloride (together with isomeric material) and 1-phenyl*cyclo*heptyl chloride were similarly obtained and contained 95% and 98% respectively of the calculated amount of chlorine.

1-Phenyl*cyclo*hexyl chloride (2·0 g.) was hydrolysed in 50% aqueous acetone (50 c.c.), the acetone was removed under reduced pressure, the residue was extracted with ether, and the extracts were dried (Na_2SO_4); evaporation of the ether left 1-phenyl*cyclo*hexanol (1·7 g.), m. p. 58—59°, m. p. and mixed m. p. 61—62°, after one recrystallisation from ligroin. Similarly, 1-phenyl*cyclo*heptanol (1·6 g.), m. p. 21—23°, m. p. and mixed m. p. 24—25°, after one recrystallisation from light petroleum, was obtained from 1-phenyl*cyclo*heptyl chloride (2·0 g.).

Addition of *cyclo*hexanone to phenylmagnesium bromide and decomposition of the product with 10% ammonium chloride solution gave 1-phenyl*cyclo*hexanol,[8] b. p. 109—110°/0·4 mm. with slight decomposition, and m. p. 61—62° after recrystallisation from ligroin. 1-Phenyl-*cyclo*heptanol,[9] b. p. 119—120°/0·4 mm. with slight decomposition, and m. p. 24—25° after recrystallisation from light petroleum, was similarly obtained from *cyclo*heptanone. This ketone, b. p. 179—180°/760 mm., was separated from the product of reaction of *cyclo*hexanone with diazomethane [10] as its semicarbazone, m. p. 163—164°. 1-*o*-Tolyl*cyclo*hexanol, b. p. 150—151°/15 mm., was obtained from *o*-tolylmagnesium bromide and *cyclo*hexanone.[11]

[8] Sabatier and Mailhe, *Ann. Chim.* (*France*), 1907, **10**, 546.
[9] Pines, Edeleanu, and Ipatieff, *J. Amer. Chem. Soc.*, 1945, **67**, 2195.
[10] Kohler, Tischler, Potter, and Thompson, *ibid.*, 1939, **61**, 1057.
[11] Sherwood, Short, and Stansfield, *J.*, 1932, 1833.

1-Phenyl*cyclo*pentene (16 g.), b. p. 107—108°/12 mm. (from metallic sodium), m. p. 22—23°, was afforded by stirring 1-phenyl*cyclo*pentanol (20 g.) with 90% formic acid (100 c.c.) for an hour at room temperature. The olefin formed an upper layer which was separated and washed successively with water, dilute aqueous sodium carbonate, and water. 1-Phenyl*cyclo*hexene,[8] b. p. 128—129°/19 mm., 1-phenyl*cyclo*heptene,[9] b. p. 115—116°/10 mm., 1-*o*-*tolyl*cyclo*pentene*, b. p. 116—117°/30 mm. (Found: C, 90·8; H, 8·8. $C_{12}H_{14}$ requires C, 91·1; H 8·9%), and 1-*o*-tolyl*cyclo*hexene,[11] b. p. 136—137°/25 mm., were similarly obtained. Their ultraviolet absorption spectra are given in Table 5.

TABLE 5.

	$\lambda_{max.}$ (Å)	ε		$\lambda_{max.}$ (Å)	ε
1-Phenyl*cyclo*pentene	2540	12,600	1-*o*-Tolyl*cyclo*pentene	2480	9800
1-Phenyl*cyclo*hexene	2480	11,100	1-*o*-Tolyl*cyclo*hexene	2450 *	4000
1-Phenyl*cyclo*heptene	2470	11,500			

* No maximum between 2100 and 3000 Å.

Determination of Rates of Ethanolysis of the Chlorides.—The sampling method described by Hughes, Ingold, and Taher [12] was used. The ethanol was purified in the manner described by Lund and Bjerrum [13] and the chlorides were used immediately after removal of the solvent in which they were prepared. Distillation of the chlorides under reduced pressure caused considerable decomposition and gave distillates containing much less halogen than was required. Before and after distillation each chloride gave rate constants which did not differ by more than the usual experimental error (*ca.* 3%). A flask, fitted with ground-in stopper, was charged with absolute ethanol (150 c.c.) and placed in a thermostat at a selected temperature. After 30 min., sufficient chloride to provide an approximately 0·05M-solution was added and the solution was vigorously shaken. At selected intervals of time samples (10 c.c.) were pipetted into ice-cold acetone (100 c.c.) and titrated with 0·05N-sodium hydroxide with lacmoid as indicator. Solvolysis was allowed to proceed to completion. The rate coefficients were derived from the equation $k = (1/t) \ln (T_\infty - T_0)/(T_\infty - T_t)$, in which the symbols have their usual significance. Each reaction was duplicated at two different temperatures. The parameters of the Arrhenius equation are listed in Table 1.

Amines.—1-Phenylpyrrolidine, b. p. 124—126°/16 mm. (picrate,[14] m. p. 116°), was obtained in 62% yield by reduction of *N*-phenylsuccinimide with lithium aluminium hydride, and 1-phenylpiperidine, b. p. 116—118°/12 mm. (picrate,[15] m. p. 148°), was similarly obtained in 62% yield from *N*-phenylglutarimide. 1-*o*-Tolylpyrrolidine, b. p. 116—118°/10 mm. [*picrate*, m. p. 138° (Found: N, 14·2. $C_{17}H_{18}O_7N_4$ requires N, 14·4%)], and 1-*o*-tolylpiperidine, b. p. 115—116°/10 mm. [*picrate*, m. p. 150° (Found: N, 13·8. $C_{18}H_{20}O_7N_4$ requires N, 13·9%)], were similarly obtained. 1-Methylpyrrolidine, b. p. 77°, was obtained by reduction ($LiAlH_4$) of *N*-methylsuccinimide, and 1-methylpiperidine in the manner described by Clarke, Gillespie, and Weisshaus.[16] 1-Methylaza*cyclo*heptane, b. p. 146° [picrate, m. p. 202° (Found: N, 17·4. Calc. for $C_{13}H_{18}O_7N_4$: N, 17·6%)], was given by reduction ($LiAlH_4$) of *N*-methyl-ε-hexanolactam, the product of methylation of ε-hexanolactam by Hepp's method.[17] Indoline, b. p. 101—102°/13 mm. (picrate,[18] m. p. 175°), was obtained by demethylation of its *N*-methyl derivative [19] (picrate, m. p. 166°), by hydriodic acid and phosphorus. 1 : 2 : 3 : 4-Trtrahydroquinoline, b. p. 248—250°, was afforded by hydrolysis of its benzoyl derivative,[20] m. p. 75°, and its *N*-methyl derivative (picrate, m. p. 144°) by reduction [21] of quinoline methiodide by tin and hydrochloric acid. Tetrahydrohomoquinoline, b. p. 119—121°/11 mm., m. p. 33° (picrate,[22] m. p. 182°), was obtained by reduction ($LiAlH_4$) of homohydrocarbostyril, the product of Beckmann rearrangement of the toluene-*p*-sulphonate of α-tetralone oxime: the sulphonate and the equivalent amount of sodium acetate were dissolved in warm glacial acetic acid, and water was

[12] Hughes, Ingold, and Taher, *J.*, 1940, 949.
[13] Lund and Bjerrum, *Ber.*, 1931, **64**, 210.
[14] Craig and Hixon, *J. Amer. Chem. Soc.*, 1930, **52**, 807.
[15] von Braun, *Ber.*, 1907, **40**, 3920.
[16] Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571.
[17] Hepp, *Ber.*, 1877, **10**, 328.
[18] von Braun and Sobecki, *Ber.*, 1911, **44**, 2159.
[19] Koizumi, Komaki, and Titan, *Bull. Chem. Soc. Japan*, 1938 **17**, 645; Wenzing, *Annalen*, 1887, **239**, 239.
[20] von Braun and Stendorff, *Ber.*, 1904, **37**, 4726.
[21] Decker, *Ber.*, 1903, **36**, 2569.
[22] von Braun and Bartsch, *Ber.*, 1912, **45**, 3376.

added until the mixture was turbid; as reaction proceeded the turbidity disappeared and more water was gradually added. The required compound, m. p. 139—140°, separated when the mixture was cooled. Its *N*-methyl derivative was afforded by addition of methyl iodide to the sodio-derivative in toluene and gave tetrahydro-1-methylhomoquinoline, b. p. 116—117°/15 mm. (picrate,[23] m. p. 140°), by reduction ($LiAlH_4$).

Determination of Basic Strengths.—The procedure was similar to that described by Davis and Addis.[24] Solutions of the amines in 50% (by volume) aqueous ethanol at 20·0° were titrated electrometrically with a standard solution of hydrogen chloride in the solvent. The amines were purified *via* their picrates and were redistilled before use. The values of pK_a are accurate within ±0·05 unit.

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[23] von Braun and Seemann, *Ber.*, 1922, **55**, 3824.
[24] Davis and Addis, *J.*, 1937, 1622.

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90. *Triterpenoids. Part XLVII.* The Constitution of Some Compounds Obtained by the Dehydration of β-Amyrin and Related Alcohols: Further Observations on the Stereochemistry of α-Amyrin.*

By G. G. ALLAN, M. B. E. FAYEZ, F. S. SPRING, and ROBERT STEVENSON.

Experiments are described which establish the steric identity of all the ring junctions in the ursane and the oleanane group of pentacyclic triterpenoids.

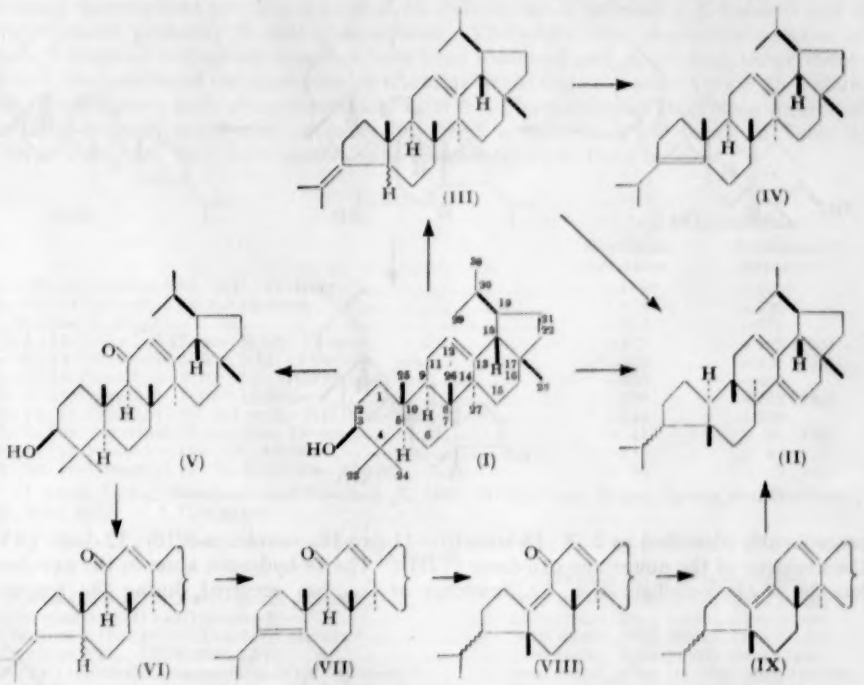
THE hydrocarbon "*l*-α-amyradiene," which is obtained in high yield by treatment of α-amyrin (I) in benzene with phosphoric oxide at room temperature, has been identified as 5 : 8α : 9β-trimethyl-10α-novursa-12 : 14-diene (II). This reaction involves contraction of ring A and migration of three axial methyl groups and one axial hydrogen atom, and is considered to be fully synchronous (Fayez, Grigor, Spring, and Stevenson, *J.*, 1955, 3378). In contrast, the same treatment of β-amyrin gives an oil, the ultraviolet absorption of which has an ill-defined single maximum (2420—2500 Å) of low intensity, whereas the crystalline "*l*-diene" (II) derived from α-amyrin has a spectrum with three intense, well-defined maxima, the principal band of which is at 2400 Å. The "*l*-diene" (II) is also obtained by treatment of α-amyrin (or its acetate) with hydriodic–acetic acid, but similar treatment of β-amyrin gives an oil, the ultraviolet absorption of which shows that it does not contain an appreciable amount of a conjugated diene.

During the investigation which led to the elucidation of the structure of the "*l*-diene" (II), it was shown that 8 : 10 : 14-trimethyl-11-oxonovursa-3(5) : 12-diene (VII) [obtained from 11-oxours-12-en-3β-ol (V) *via* the isomeric 11-oxo-3(4) : 12-diene (VI)] is isomerised to 5 : 8 : 14-trimethyl-11-oxonovursa-9(10) : 12-diene (VIII) by hydriodic–acetic acid. The oxo-diene (VIII) is reduced by lithium aluminium hydride to the non-conjugated 5 : 8 : 14-trimethylnovursa-9(10) : 12-diene (IX) which with hydrochloric–acetic acid gives the conjugated diene (II). The last reaction, described by Allan, Spring, Stevenson, and Strachan (*J.*, 1955, 3371), is the most remarkable stage in the series of reactions included in the conversion of α-amyrin into the "*l*-diene" (II), remarkable in that conjugation does not occur by the most direct route, but only as a consequence of the movement of two axial methyl groups. It emerges from the discussion below that this is the critical stage in the conversion of α-amyrin into a conjugated 12 : 14-diene.

Allan *et al.* (*loc. cit.*) showed that dehydration of α-amyrin by phosphorus pentachloride gives 8 : 10 : 14-trimethyl-5ξ-novursa-3(4) : 12-diene (III) which is isomerised to the 3(5) : 12-diene (IV) by treatment with trichloroacetic acid. It was also found that treatment of the diene (III) with boron trifluoride–acetic acid yields the conjugated diene (II).

* Part XLVI, following note.

Short treatment of β-amyrin (X) with phosphorus pentachloride gives "β-amyrilene-I" (Vesterberg, *Ber.*, 1887, **20**, 1242; 1890, **23**, 2189; Ruzicka, Silbermann, and Furter, *Helv. Chim. Acta*, 1932, **15**, 482; Winterstein and Stein, *Annalen*, 1933, **502**, 223) which, as we expected, is 8 : 10 : 14-trimethyl-5ξ-novoleana-3(4) : 12-diene (XI),* since on ozonolysis



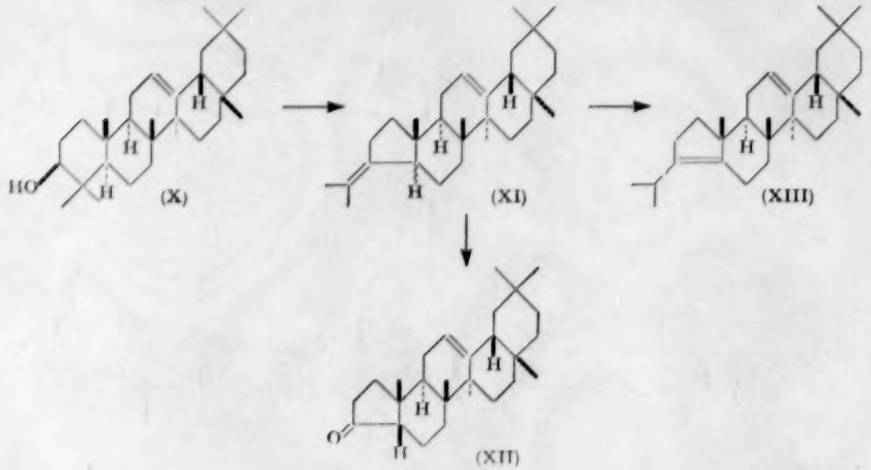
it yields acetone and a ketone, $C_{27}H_{42}O$ (XII). As in the case of its novursane analogue, a consideration of molecular-rotation relations shows that rings A and B in the ketone (XII) are *cis*-β-fused. Treatment of the 3(4) : 12-diene (XI) with trichloroacetic acid (or prolonged treatment of β-amyrin with phosphorus pentachloride) yields an isomer "β-amyrilene-III" (Dieterle, Brass, and Schaal, *Arch. Pharm.*, 1937, **275**, 557). A comparison of the specific rotations (Table 1) supports the view that this isomer is 8 : 10 : 14-trimethyl-novoleana-3(5) : 12-diene (XIII). This comparison also shows that the 12 : 13-double bond does not move during the conversion of β-amyrin into the two dienes (XI) and (XIII).

An important difference in behaviour of the 3(4) : 12-dienes derived from α- and β-amyrin is to be noted. Whereas the novursadiene (III) gives the conjugated diene (II) when

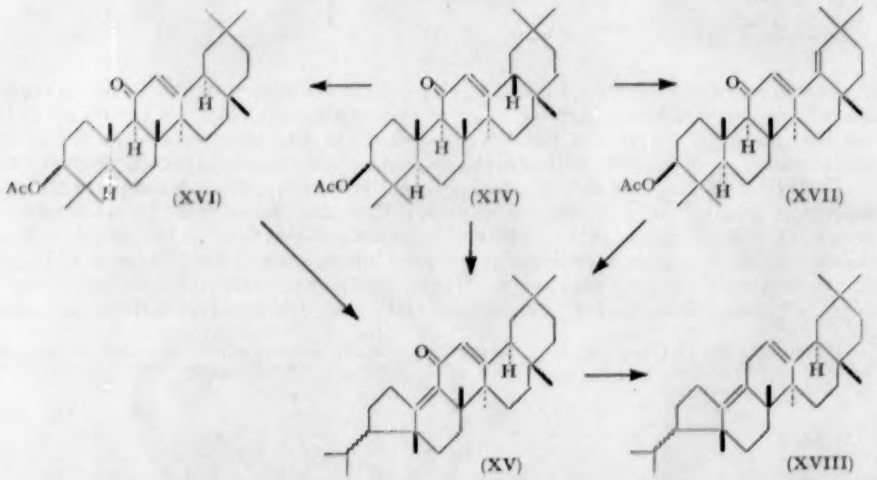
* Following the system adopted for naming ring-A contracted derivatives of ursane (Allan *et al.*, *loc. cit.*), the hydrocarbon $C_{27}H_{44}$ having the constitution and stereochemistry represented by (*A*) is called novoleanane.

treated with boron trifluoride, similar treatment of the novoleanadiene (XI) gives an oil, the ultraviolet absorption of which indicates the presence of only a small proportion of a conjugated diene.

When 11-oxo-olean-12-en-3β-yl acetate (XIV) is refluxed with hydriodic–acetic acid, it gives an oxo-diene which shows maximal absorption at 2060, 2560, and 2870 Å, and is



consequently identified as 5 : 8 : 14-trimethyl-11-oxo-18α-novoleana-9(10) : 12-diene (XV), the analogue of the novursane oxo-diene (VIII). The 18-hydrogen atom in the oxo-diene has the stable α-configuration, *i.e.*, inversion at $C_{(18)}$ has occurred during the reaction,



because this compound is also obtained by treatment of 11-oxo-18α-olean-12-en-3β-yl acetate (XVI) (Budziarek, Manson, and Spring, *J.*, 1951, 3336) with hydriodic acid. The same treatment of 11-oxo-oleana-12 : 18-dien-3β-yl acetate (XVII) (Picard and Spring, *J.*, 1941, 35) also gives the conjugated oxo-diene (XV); in this reaction reduction of the

terminal ethylene bond has occurred, the 18-hydrogen atom adopting the α-configuration, in addition to ring contraction and movement of the methyl group from $C_{(10)}$ to $C_{(5)}$.

The ultraviolet absorption of a compound containing a $>C{:}C\cdot\overset{\overset{O}{\|}}{C}\cdot C{:}C<$ (conjugated enonene) chromophore provides a method for differentiating between a di-transoid and a cisoid-transoid geometry in this chromophore. The ultraviolet absorption spectra of many di-transoid conjugated enonenes have been measured and, apart from minor differences in the position of the maximum attributable to the degree of substitution, they show a single absorption peak at approximately 2400 Å. The ultraviolet absorption spectra of the cisoid-transoid conjugated enonenes described in this Series are shown in Table 2. Without exception, they have spectra with the characteristic three maxima.

TABLE 1.

	$[\alpha]_D$ (in chloroform)	
	Novursane derivative [1]	Novoleanane derivative [2]
8 : 10 : 14-Trimethyl-5ξ-, 3(4) : 12-diene	+109°	+110°
8 : 10 : 14-Trimethyl-, 3(5) : 12-diene	+123	+120
Ketone, $C_{27}H_{42}O$	+210	+215
5 : 8 : 14-Trimethyl-11-oxo-, 9(10) : 12-diene	+171	+122 (18α)
5 : 8 : 14-Trimethyl-, 1(10) : 9(11) : 12-triene	−358	−450 (18α)
5 : 8 : 14-Trimethyl-, 9(10) : 11 : 13(18)-triene	−450	−400
5 : 8 : 14-Trimethyl-, 9(10) : 12-diene	+120	+103 (18α)
8 : 10 : 14-Trimethyl-5ξ-, 3(4 or 5) : 9(11) : 12-triene	+445	+356
5 : 8α : 9β-Trimethyl-12-oxo-10α-, 13-ene	− 41	− 32 (18ξ)
5 : 8α : 9β-Trimethyl-10α-, 12 : 14-diene	−110	− 83 (18ξ)
5 : 8α : 9β-Trimethyl-12 : 15-dioxo-10α-, 13-ene	+ 86	− 7 (18ξ)

[1] Allan, Spring, Stevenson, and Strachan, *J.*, 1955, 3371; Fayez, Grigor, Spring, and Stevenson, *J.*, 1955, 3378. [2] This paper.

TABLE 2.

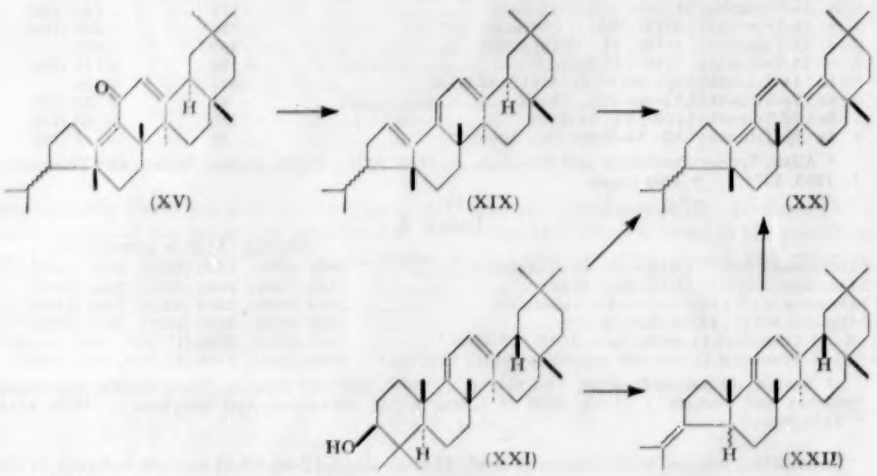
	Maxima (Å) (ε in parentheses)
12-Oxo-oleana-9(11) : 13(18)-dien-3β-yl acetate [1]	2080 (9000), 2600 (9250), 2950 (8450)
12-Oxo-oleana-9(11) : 13(18)-dien-3β-ol [1]	2100 (7600), 2600 (8600), 2950 (8100)
12-Oxoursa-9(11) : 13(18)-dien-3β-yl acetate [2]	2070 (9000), 2610 (9700), 2940 (8100)
12-Oxoursa-9(11) : 13(18)-dien-3β-ol [2]	2080 (8050), 2630 (9600), 2950 (7400)
5 : 8 : 14-Trimethyl-11-oxonovursa-9(10) : 12-diene [3]	2040 (9900), 2580 (11,000), 2900 (10,200)
5 : 8 : 14-Trimethyl-11-oxo-18α-novoleana-9(10) : 12-diene [4]	2060 (6900), 2560 (10,700), 2870 (9300)

[1] Beaton, Johnston, McKean, and Spring, *J.*, 1953, 3600. [2] Beaton, Shaw, Spring, Stevenson, Strachan and Stewart, *J.*, 1955, 2606. [3] Allan, Spring, Stevenson, and Strachan, *J.*, 1955, 3371. [4] This paper.

Thus, when treated with hydriodic acid, 11-oxo-olean-12-en-3β-yl acetate behaves in the same way as 11-oxours-12-en-3β-yl acetate, apart from inversion at $C_{(18)}$ in the former case. In each case, contraction of ring A occurs and conjugation is subsequently achieved by the transfer of a methyl group from $C_{(10)}$ to $C_{(5)}$. Moreover, with one important exception, there is a general similarity between the reactions of the conjugated enonenes (VIII) and (XV). Treatment of 5 : 8 : 14-trimethyl-11-oxo-18α-novoleana-9(10) : 12-diene (XV) with lithium aluminium hydride at 0° gives 5 : 8 : 14-trimethyl-18α-novoleana-1(10) : 9(11) : 12-triene (XIX). This conjugated triene is strongly lævorotatory ($[\alpha]_D$ −450°) and it shows intense maximal absorption at 3150 Å. It is similar in these respects to the analogously constituted novursatriene (Allan *et al.*, *loc. cit.*) and ergosta-5 : 7 : 14 : 22-tetraenyl acetate ($[\alpha]_D$ −322°, $\lambda_{max.}$ 3190 Å, ε 15,000) (Barton and Bruun, *J.*, 1951, 2728). The novoleanatriene (XIX) is isomerised by mineral acid to 5 : 8 : 14-trimethylnovoleana-9(10) : 11 : 13(18)-triene (XX) which shows three maxima in the absorption spectrum, the principal band in which is at 2950 Å (ε 35,000). The triene (XX) is also obtained by treatment of oleana-9(11) : 12-dien-3β-ol (XXI) (Picard and Spring, *J.*, 1940, 1198) with phosphoric oxide. Dehydration of the dienol (XXI) by phosphorus pentachloride gives a triene which shows the characteristic ultraviolet spectrum of a homoannular diene and which we formulate as either 8 : 10 : 14-trimethyl-5ξ-novoleana-3(4) : 9(11) : 12-triene (XXII) or the 3(5) : 9(11) : 12-triene isomer. This hydrocarbon is isomerised by trichloroacetic acid to the conjugated

triene (XX). The various methods described above for the conversion of β-amyrin into the conjugated triene (XX) duplicate those used for the conversion of α-amyrin into 5 : 8 : 14-trimethylnovursa-9(10) : 11 : 13(18)-triene (Allan *et al.*, *loc. cit.*) and we observe that this series of reactions does not involve the movement of the methyl groups attached to $C_{(8)}$ and $C_{(14)}$.

The exception to the rule of general similarity between the reactions of the isomeric conjugated enonenes (VIII) and (XV) and their derivatives, to which reference was made above, is to be found in the following reactions. Reduction of the conjugated enonene (XV) with a refluxing solution of lithium aluminium hydride in ether gives 5 : 8 : 14-trimethyl-18α-novoleana-9(10) : 12-diene (XVIII), the structure of which follows from its method of formation and from the fact that it does not show selective absorption in the ultraviolet region above 2200 Å. Treatment of the non-conjugated diene (XVIII) with hydrochloric–acetic acid, in conditions which convert the analogous non-conjugated novursadiene (IX) into the conjugated "*l*-diene" (II) in high yield, failed to give a conjugated diene. This difference can be defined as the inability of the 18α-oleanane derivative (XVIII) to undergo a reaction involving migration of the methyl groups attached to $C_{(8)}$ and $C_{(14)}$ to $C_{(9)}$ and $C_{(8)}$ respectively.

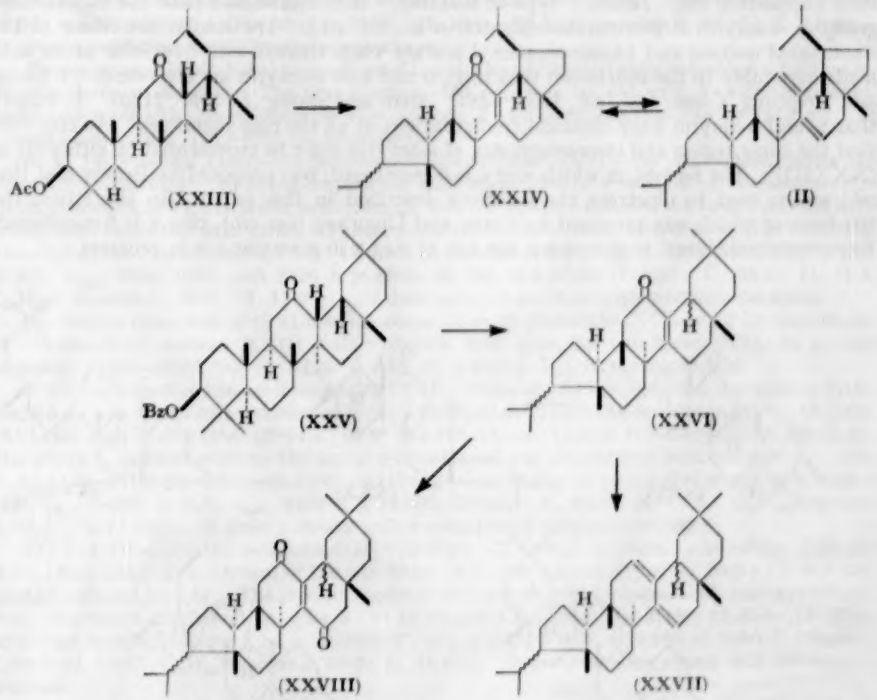


At this stage of the investigation, it appeared probable that the driving force responsible for the final stages of the conversion of α-amyrin into 5 : 8α : 9β-trimethyl-10α-novursa-12 : 14-diene (II) was a conformational constraint imposed by the (stable) *cis*-locking of rings D/E (cf. Beton and Halsall, *Chem. and Ind.*, 1954, 1560) and that the failure of β-amyrin to give a similarly constituted diene is due to the fact that the *cis*-locking of rings D/E in β-amyrin is not stable in an acid medium. We argued that, if this view is correct, it should be possible to achieve an "*l*-diene" type of reaction starting from a β-amyrin derivative in which the *cis*(β)-junction of rings D/E is locked. Experiments were designed to test this hypothesis.

Fayez *et al.* (*loc. cit.*) found that treatment of 12-oxoursanyl acetate (XXIII) with hydriodic–acetic acid gives 5 : 8α : 9β-trimethyl-12-oxo-10α-novurs-13-ene (XXIV), a reaction analogous to the conversion of α-amyrin into the conjugated diene (II), since it includes contraction of ring A and synchronous movement of axial methyl groups from $C_{(10)}$, $C_{(8)}$, and $C_{(14)}$ to $C_{(5)}$, $C_{(9)}$, and $C_{(8)}$ respectively. The relation of the αβ-unsaturated ketone (XXIV) and the conjugated diene (II) was confirmed by their interconversion. We find that treatment of 12-oxo-oleananyl benzoate (XXV) with hydriodic–acetic acid gives 5 : 8α : 9β-trimethyl-12-oxo-10α : 18β-novolean-13-ene (XXVI), the structure of which

followed from its properties and the reactions described below. It shows maximal absorption at 2600 Å (ε 10,000) thus confirming the view that the chromophore is an ααββ-tetrasubstituted αβ-unsaturated ketone group. Reaction of the αβ-unsaturated ketone (XXVI) with lithium aluminium hydride and treatment of the product with hydrochloric acid gave 5 : 8α : 9β-trimethyl-10α : 18ξ-novoleana-12 : 14-diene (XXVII). This diene has three maxima in its absorption spectrum [$\lambda_{max.}$ 2340 (ε 15,000), 2410 (ε 16,000), and 2490 Å (ε 10,700)]. It is lævorotatory ($[\alpha]_D$ −83°) and in these respects and in its origin it is the exact analogue of the "*l*-diene" (II). The relations implied by the formulations proposed for the αβ-unsaturated ketone (XXVI) and the conjugated diene (XXVII) were confirmed by oxidation of the former to a transoid enedione, 5 : 8α : 9β-trimethyl-12 : 15-dioxo-10α : 18ξ-novolean-13-ene (XXVIII) which shows an absorption maximum at 2780 Å (ε 8000).*

Further support for the view that the driving force supporting reactions (XXIII) ⟶ (XXIV) and (XXV) ⟶ (XXVI) is the constraint imposed by a *cis*(β)-locking of rings D and E was obtained by a study of 12-oxo-18α-oleanan-3β-yl acetate (XXIX) (Budziarek *et al.*,

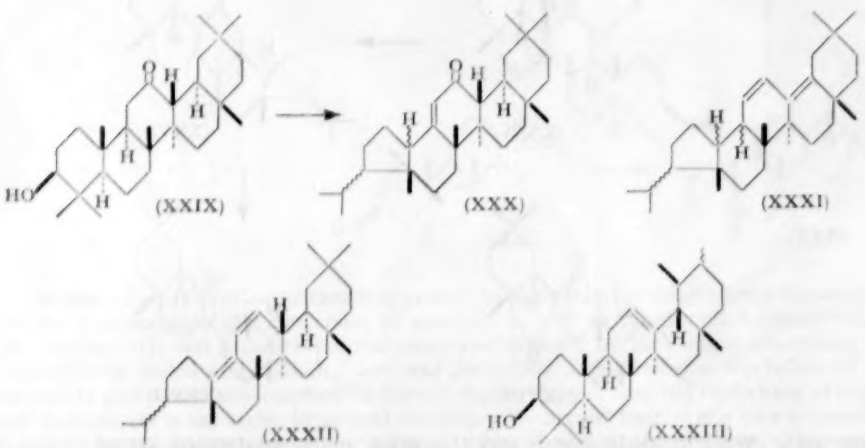


loc. cit.). With hydriodic–acetic acid this gives an αβ-unsaturated ketone, which we formulate as 5 : 8 : 14-trimethyl-12-oxo-10ξ : 18α-novolean-9(11)-ene (XXX) since it shows an absorption maximum at 2440 Å (ε 11,200) and in this respect differs markedly from the two αβ-unsaturated ketones (XXIV) and (XXVI). Unlike the last two compounds, moreover, the 9(11)-en-12-one (XXX) is dextrorotatory. The structure of (XXX) was confirmed

* It is possible that an ultimate consequence of the conversion of the saturated keto-benzoate (XXV) into the αβ-unsaturated ketone (XXVI) is inversion at $C_{(10)}$; the configuration at this centre in the related compounds (XXVI), (XXVII), and (XXVIII) is undecided for the time being. It may be of significance that there is a general correspondence in the specific rotations of analogous novoleanane and novursane derivatives (Table 1) with the exception of the enedione (XXVIII) and its novursane analogue.

by reduction with lithium aluminium hydride followed by treatment of the product with acetic anhydride and sodium acetate, which yielded a hydrocarbon which, we believe, is either the 11 : 13(18)-diene (XXXI) or the 9 : 11-diene (XXXII), since, like oleana-11 : 13(18)-dienyl acetate, it shows three maxima [λ 2450, 2520, and 2600 Å (ε 24,600, 27,000, and 26,000)].

We now summarise the more important implications of the comparison of the behaviour of analogous oleanane and ursane derivatives made above. The *cis*-locking of rings D and E in β-amyrin is unstable in that, if a carbonyl group or a double bond is immediately adjacent to $C_{(18)}$, inversion to a *trans*-fused 18α-oleanane isomer can occur. In our opinion, a reaction strictly analogous to the conversion of α-amyrin into the "*l*-diene" is not observed with β-amyrin, because the 12 : 13-double bond in this compound is not stable to strong acid. On the other hand, the locking of rings D and E in α-amyrin is stable (Beaton, Spring, Stevenson, and Strachan, *J.*, 1955, 2610); urs-12-en-3-one, unlike olean-12-en-3-one, is recovered unchanged after vigorous treatment with mineral acid (Davy, Halsall, and Jones, *J.*, 1951, 458). The conversion of 12-oxo-oleananyl acetate, but not its 18α-epimer, into a 12-oxo-13 : 14-ene in our opinion shows that the *cis*-locking of rings D and E is the driving force supporting the "*l*-diene" type of reaction. It is established that the $C_{(17)}$-methyl group in α-amyrin is β-orientated (Beaton *et al.*, *loc. cit.*). The similar behaviour of 12-oxoursanyl acetate and 12-oxo-oleananyl acetate when treated with hydriodic–acetic acid leads inevitably to the conclusion that rings D and E in α-amyrin are *cis*-β-fused (cf. Corey and Ursprung, *Chem. and Ind.*, 1954, 1387; Allan and Spring, *J.*, 1955, 2125). It follows that α- and β-amyrin have identical configurations at all the ring junctions. We conclude that the constitution and stereochemistry of α-amyrin must be represented by either (I) or (XXXIII). The former, in which ring E is 5-membered, was proposed by Beaton *et al.* (*loc. cit.*) and is used to illustrate the reactions described in this paper. In the latter, the 20α-form of which was proposed by Corey and Ursprung (*loc. cit.*), ring E is 6-membered. Experiments designed to determine the size of ring E in α-amyrin are in progress.



Experimental

Rotations were measured in $CHCl_3$ and ultraviolet absorption spectra in EtOH solutions. Grade II alumina and light petroleum, b. p. 60—80°, were used for chromatography.

8 : 10 : 14-*Trimethyl*-5ξ-*novoleana*-3(4) : 12-*diene* ("β-*Amyrilene*-I") (XI).—β-Amyrin (5·0 g.) was added to a suspension of phosphorus pentachloride (3·2 g.) in light petroleum (b. p. 60—80°; 40 c.c.), and the mixture shaken for 30 min. and filtered. The filtrate was washed with warm water, dried (Na_2SO_4), and evaporated, and the residue crystallised from acetone to give 8 : 10 : 14-trimethyl-5ξ-novoleana-3(4) : 12-diene (XI) as needles, m. p. 167—172°, $[\alpha]_D$ +110°

(*c* 1·8), ε 9200 at 2080 Å (Found : C, 88·5; H, 12·0. Calc. for $C_{30}H_{48}$: C, 88·2; H, 11·8%). It gives a yellow colour with tetranitromethane.

Treatment of β-amyrin in benzene with phosphoric oxide, as described for the preparation of the "*l*-diene" from α-amyrin (Vesterberg, *Ber.*, 1891, **24**, 3835), gave a gum, $\lambda_{max.}$ 2070 and 2420 Å (ε 4500 and 4400).

8 : 10 : 14-Trimethylnovoleana-3(5) : 12-diene ("β-amyrilene-III") (XIII) was obtained as described by Dieterle, Brass, and Schaal (*loc. cit.*), by treatment either of β-amyrin with phosphorus pentachloride in light petroleum (b. p. 60—80°) or of the isomer (XI) with trichloroacetic acid; it crystallised from chloroform–methanol as plates, m. p. 102—104°, $[\alpha]_D$ +120° (*c* 1·8) and gives a yellow colour with tetranitromethane.

Ozonolysis of 8 : 10 : 14-*Trimethyl*-5ξ-*novoleana*-3(4) : 12-*diene* (XI).—A solution of the diene (XI) (1·0 g.) in dry chloroform (200 c.c.) was treated at −40° with ozone (1·2 mols.). After attaining room temperature, the mixture was stirred with zinc dust (3 g.) and acetic acid (50 c.c.) for 1 hr. The filtered solution was washed with water (3 × 500 c.c., see below), the chloroform removed under reduced pressure, and the residue dissolved in light petroleum and chromatographed. Light petroleum (100 c.c.) eluted unchanged diene (XI) (263 mg.). The fraction (427 mg.) eluted with benzene–light petroleum (1 : 4; 300 c.c.) was recrystallised five times from chloroform–methanol, to give the *ketone* (XII) as plates, m. p. 192—194°, $[\alpha]_D$ +215° (*c* 2·7), ε 5700 at 2065 Å (Found : C, 85·05; H, 10·8. $C_{27}H_{42}O$ requires C, 84·75; H, 11·1%). It gives a yellow colour with tetranitromethane.

The water washings (above) were adjusted to pH 7 by addition of sodium hydrogen carbonate, and the solution distilled. The first fraction (250 c.c.) was treated with 2 : 4-dinitrophenylhydrazine hydrochloride solution to give acetone 2 : 4-dinitrophenylhydrazone (117 mg.) as orange blades, m. p. 123—125° (no depression).

5 : 8 : 14-*Trimethyl*-11-*oxo*-18α-*novoleana*-9(10) : 12-*diene* (XV).—(*a*) Hydriodic acid (15 c.c.; *d* 1·7; distilled from hypophosphorous acid) was added to a solution of 11-oxo-olean-12-en-3β-yl acetate (5·0 g.) in acetic acid (50 c.c.), and the mixture refluxed for 16 hr., diluted with water, and extracted with ether. The product crystallised from methanol to give 5 : 8 : 14-*trimethyl*-11-*oxo*-18α-*novoleana*-9(10) : 12-*diene* as needles (1·3 g.), m. p. 191—192°, $[\alpha]_D$ +122° (*c* 2·3), $\lambda_{max.}$ 2060, 2560, and 2870 Å (ε 6900, 10,700, and 9300) (Found : C, 85·3; H, 11·3. $C_{30}H_{46}O$ requires C, 85·2; H, 11·0%). It does not give a colour with tetranitromethane.

(*b*) Similar treatment of (i) 11-oxo-18α-olean-12-en-3β-yl acetate (XVI) or (ii) 11-oxo-oleana-12 : 18-dien-3β-yl acetate (XVII) with hydriodic acid gave the oxo-diene (XV), m. p. and mixed m. p. 191—192°, $[\alpha]_D$ (i) +125° (*c* 3·1), (ii) +124° (*c* 1·7), in the same yield.

5 : 8 : 14-*Trimethyl*-18α-*novoleana*-1(10) : 9(11) : 12-*triene* (XIX).—Lithium aluminium hydride (0·5 g.) was added to a solution of 5 : 8 : 14-trimethyl-11-oxo-18α-novoleana-9(10) : 12-diene (XV) (400 mg.) in dry ether (200 c.c.) at 0° and the mixture kept at this temperature for 72 hr. The product, isolated without the use of mineral acid, was crystallised from methanol to give 5 : 8 : 14-*trimethyl*-18α-*novoleana*-1(10) : 9(11) : 12-*triene* (XIX) as plates (250 mg.), m. p. 140—142°, $[\alpha]_D$ −450° (*c* 0·9), $\lambda_{max.}$ 3150 Å (ε 14,000) (Found : C, 88·6; H, 11·5. $C_{30}H_{46}$ requires C, 88·6; H, 11·4%). It gives a strong yellow colour with tetranitromethane.

5 : 8 : 14-*Trimethyl*-18α-*novoleana*-9(10) : 12-*diene* (XVIII).—Lithium aluminium hydride (1·0 g.) was added to a solution of the oxo-diene (XV) (800 mg.) in dry ether (500 c.c.), and the mixture refluxed for 7 hr. The product, isolated without the use of mineral acid, was crystallised from chloroform–methanol, to give 5 : 8 : 14-*trimethyl*-18α-*novoleana*-9(10) : 12-*diene* (XVIII) as matted needles (400 mg.), m. p. 160—162°, $[\alpha]_D$ +103° (*c* 0·7), ε 10,500 at 2080 Å (Found : C, 88·0; H, 12·0. $C_{30}H_{48}$ requires C, 88·2; H, 11·8%). It gives a yellow colour with tetranitromethane.

Treatment of the diene (XVIII) with hydrochloric–acetic acid, under conditions used to convert the analogous novursadiene into the "*l*-diene" (II), yielded a brown gum, the ultraviolet spectrum of which had no high intensity-absorption above 2200 Å.

5 : 8 : 14-*Trimethylnovoleana*-9(10) : 11 : 13(18)-*triene* (XX).—(*a*) A solution of oleana-9(11) : 12-dien-3β-ol (XXI) (2·0 g.) in dry benzene (60 c.c.) was shaken with phosphoric oxide (3·0 g.) for 20 hr. The product, isolated in the usual way and crystallised from methanol, yielded 5 : 8 : 14-*trimethylnovoleana*-9(10) : 11 : 13(18)-*triene* (XX) as needles (600 mg.), m. p. 135—136° $[\alpha]_D$ −400° (*c* 1·8), $\lambda_{max.}$ 2860, 2950, and 3080 Å (ε 31,000, 36,000 and 25,400) (Found : C, 88·9; H, 11·7. $C_{30}H_{46}$ requires C, 88·6; H, 11·4%). It gives a red-brown colour with tetranitromethane.

(*b*) Concentrated hydrochloric acid (2 c.c.) was added to 5 : 8 : 14-trimethyl-18α-novoleana-1(10) : 9(11) : 12-triene (XIX) (50 mg.) in acetic acid (50 c.c.), and the mixture left at room

temperature for 72 hr. The product, isolated by means of ether, was crystallised from methanol to give the triene (XX) (20 mg.), m. p. 132—135° (no depression), $[\alpha]_D$ −407° (*c* 0·4).

(*c*) A solution of 5 : 8 : 14-trimethyl-11-oxo-18α-novoleana-9(10) : 12-diene (XV) (0·7 g.) (in dry ether (200 c.c.) was added dropwise to a suspension of lithium aluminium hydride (0·7 g.) in dry ether (200 c.c.), and the mixture refluxed for 2 hr. The product was worked up as usual and the residue, obtained on evaporation of the ether, dissolved in light petroleum and chromatographed. Elution with light petroleum (300 c.c.) gave a solid (147 mg.) which was crystallised from chloroform–methanol to give 5 : 8 : 14-trimethyl-18α-novoleana-9(10) : 12-diene (XVIII) as matted needles, m. p. and mixed m. p. 161—162°, $[\alpha]_D$ +101° (*c* 0·85). Further elution with the same solvent (100 c.c.) yielded a solid (33 mg.) which was not examined. Benzene–light petroleum (1 : 9; 650 c.c.) gave a fraction (464 mg.), which after repeated crystallisation from chloroform–methanol gave 5 : 8 : 14-trimethylnovoleana-9(10) : 11 : 13(18)-triene (XX) as needles, m. p. and mixed m. p. 135—136°, $[\alpha]_D$ −400° (*c* 1·8).

(*d*) A solution of 8 : 10 : 14-trimethyl-5ξ-novoleana-3(4) : 9(11) : 12-triene (XXII) (40 mg.; see below) and trichloroacetic acid (40 mg.) in chloroform (1 c.c.) was kept at room temperature for 1 hr., and the solvent removed under reduced pressure. The product, isolated by means of ether, crystallised from chloroform–methanol to yield the triene (XX) as needles, m. p. 133—134° (no depression), $[\alpha]_D$ −388° (*c* 0·60).

8 : 10 : 14-*Trimethyl*-5ξ-*novoleana*-3(4 or 5) : 9(11) : 12-*triene*.—Oleana-9(11) : 12-dien-3β-ol (0·8 g.) was shaken with phosphorus pentachloride (0·42 g.) in light petroleum (b. p. 60—80°; 25 c.c.) for 1 hr. and then refluxed for 2 min. The product, isolated in the usual way, was recrystallised five times from acetone, to give 8 : 10 : 14-*trimethyl*-5ξ-*novoleana*-3(4 or 5) : 9(11) : 12-*triene* as needles, m. p. 150—152°, $[\alpha]_D$ +356° (*c* 2·7), $\lambda_{max.}$ 2060 and 2800 Å (ε 8300 and 8000) (Found: C, 88·2; H, 11·8. $C_{30}H_{48}$ requires C, 88·6; H, 11·4%). It gives a deep red-brown colour with tetranitromethane.

5 : 8α : 9β-*Trimethyl*-12-*oxo*-10α : 18ξ-*novolean*-13-*ene* (XXVI).—Hydriodic acid (4 c.c.; *d* 1·7; distilled from hypophosphorous acid) was added to a solution of 12-oxo-oleanan-3β-yl benzoate (XIV) (1·0 g.) in acetic acid (30 c.c.), the mixture refluxed for 16 hr., diluted with water, and extracted with ether. The product was worked up in the usual way, and the crude product (0·36 g.; m. p. 155—159°) crystallised three times from aqueous methanol to give 5 : 8α : 9β-*trimethyl*-12-*oxo*-10α : 18ξ-*novolean*-13-*ene* as long plates, m. p. 171—172°, $[\alpha]_D$ −32° (*c*, 2·5), $\lambda_{max.}$ 2600 Å (ε 9700) (Found: C, 84·5; H, 11·6. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%). It does not give a colour with tetranitromethane.

5 : 8α : 9β-*Trimethyl*-10α : 18ξ-*novoleana*-12 : 14-*diene* (XXVII).—A solution of 5 : 8α : 9β-trimethyl-12-oxo-10α : 18ξ-novolean-13-ene (XXVI) (1·0 g.) in dry ether (200 c.c.) was added dropwise to a suspension of lithium aluminium hydride (1 g.) in dry ether (200 c.c.), and the mixture refluxed for 2 hr. The product (880 mg.), isolated in the usual way, gave a yellow colour with tetranitromethane and exhibited ultraviolet light absorption at 2130 Å. Concentrated hydrochloric acid (2 c.c.) was added to a solution of this solid (100 mg.) in chloroform (3 c.c.) and acetic acid (25 c.c.), and the mixture heated on the steam-bath for 30 min. On cooling, the crystalline product was collected and recrystallised from chloroform–methanol to give 5 : 8α : 9β-*trimethyl*-10α : 18ξ-*novoleana*-12 : 14-*diene* (75 mg.) as needles, m. p. 155—156°, $[\alpha]_D$ −83° (*c* 2·5), $\lambda_{max.}$ 2340 (shoulder), 2410, and 2490 (shoulder) Å (ε 15,000, 16,000, and 10,700) (Found: C, 88·1; H, 11·7. $C_{30}H_{48}$ requires C, 88·2; H, 11·8%). It gives an orange-brown colour with tetranitromethane.

5 : 8α : 9β-*Trimethyl*-12 : 15-*dioxo*-10α : 18ξ-*novolean*-13-*ene* (XXVIII).—(*a*) Chromium trioxide (0·6 g.) in 90% acetic acid (7 c.c.) was added to 5 : 8α : 9β-trimethyl-12-oxo-10α : 18ξ-novolean-13-ene (XXVI) (1·0 g.) in acetic acid (72 c.c.), and the mixture stirred on the steam-bath for 1 hr. After the addition of methanol, the product was isolated in the usual way, and its solution in benzene–light petroleum (3 : 7) was chromatographed on alumina. Elution with the same solvent (200 c.c.) yielded a solid (600 mg.), which, after four recrystallisations from aqueous methanol gave 5 : 8α : 9β-*trimethyl*-12 : 15-*dioxo*-10α : 18ξ-*novolean*-13-*ene* as yellow needles, m. p. 145—146°, $[\alpha]_D$ −8°, −7° (*c* 2·2, 1·9), $\lambda_{max.}$ 2220 and 2780 Å (ε 3100 and 8000) (Found: C, 82·3; H, 10·7. $C_{30}H_{46}O_2$ requires C, 82·1; H, 10·6%). It does not give a colour with tetranitromethane.

(*b*) A solution of the αβ-unsaturated ketone (XXVI) (120 mg.) in 10% ethanolic potassium hydroxide (100 c.c.) was refluxed for 2 hr. The product was isolated by using ether, and crystallised four times from aqueous methanol, to give the enedione (XXVIII) as yellow needles, m. p. 144—145° (no depression), $[\alpha]_D$ −7° (*c* 2·4), $\lambda_{max.}$ 2220 and 2770 Å (ε 3200 and 7700).

Action of Hydriodic Acid on 12-*Oxo*-18α-*oleanan*-3β-*yl Acetate* (XXIX).—Hydriodic acid

(4 c.c.; *d* 1·7; distilled from hypophosphorous acid) was added to a solution of the saturated keto-acetate (XXIX) (1·0 g.) in acetic acid (20 c.c.), and the mixture refluxed for 16 hr. and worked up in the usual way. The product was dissolved in light petroleum and chromatographed on alumina. Benzene–light petroleum (1 : 9; 100 c.c.) eluted a fraction (165 mg.) which was crystallised from chloroform–methanol to give 8 : 10 : 14-*trimethyl*-12-*oxo*-18α-*novolean*-3(4 or 5)-*ene* as long plates, m. p. 181—182°, $[\alpha]_D$ +50° (*c* 2·5), ε 6200 at 2100 Å (Found: C, 85·0; H, 11·6. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%). It gives a yellow colour with tetranitromethane. Elution with the same solvent (400 c.c.) and benzene–light petroleum (3 : 7; 50 c.c.) gave a mixture (267 mg.). Further elution with benzene–light petroleum (3 : 7; 200 c.c.) yielded a solid (106 mg.), which was crystallised from chloroform–methanol to give 5 : 8 : 14-*trimethyl*-12-*oxo*-10ξ : 18α-*novolean*-9(11)-*ene* (XXX) as needles, m. p. 247—248°, $[\alpha]_D$ +99° (*c* 0·9), $\lambda_{max.}$ 2440 Å (ε 11,200) (Found: C, 85·1; H, 11·6. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%). It does not give a colour with tetranitromethane.

Preparation of the Heteroannular Diene (XXXI) *or* (XXXII) *from* 5 : 8 : 14-*Trimethyl*-12-*oxo*-10ξ : 18α-*novolean*-9(11)-*ene* (XXX).—A solution of the αβ-unsaturated ketone (XXX) (55 mg.) in dry ether (50 c.c.) was added to lithium aluminium hydride (100 mg.) in ether (50 c.c.), and the mixture refluxed for 2 hr. and worked up in the usual way. A solution of the product in acetic anhydride (20 c.c.) containing freshly fused sodium acetate (100 mg.) was refluxed for 2 hr. Isolation through ether, and crystallisation from chloroform–methanol, gave the *diene* (XXXI) or (XXXII) as plates, m. p. 178—179°, $[\alpha]_D$ +30° (*c* 0·5), $\lambda_{max.}$ 2450 (shoulder), 2520, and 2600 (shoulder) Å (ε 24,600, 27,000, and 20,000) (Found: C, 88·1; H, 12·2. $C_{30}H_{48}$ requires C, 88·2; H, 11·8%). It gives a dark brown colour with tetranitromethane.

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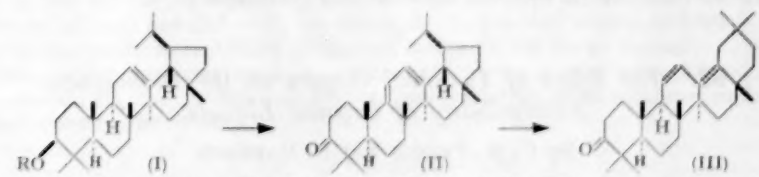
NOTES.

91. *Triterpenoids. Part XLVI.* The Conversion of Ursa*-9(11) : 12-*dien*-3-*one into Oleana*-11 : 13(18)-*dien*-3-*one.*

By J. I. SHAW, F. S. SPRING, and ROBERT STEVENSON.

THE conversion of three dienes derived from α-amyrin into a β-amyrin derivative, and other arguments, led Beaton, Spring, Stevenson, and Strachan [1] to propose the formula (I; R = H) for α-amyrin. The most readily available of the three compounds converted into an oleanane isomer, namely, ursa-9(11) : 12-dien-3β-yl acetate,[2] on treatment with hydrochloric–acetic acid mixture gave only 10% of pure oleana-11 : 13(18)-dien-3β-yl



acetate,[1] probably owing partly to the instability of the 3β-acetoxy-group under the strongly acid conditions where secondary reactions, such as contraction of ring A, intervene. This important argument is now supported by conversion of ursa-9(11) : 12-dien-3-one (II) into oleana-11 : 13(18)-dien-3-one (III) in 65% (crude) and 30% (pure) yield.

* Part XLV, *J.*, 1955, 3992.

[1] Beaton, Spring, Stevenson, and Strachan, *J.*, 1955, 2610.
[2] Ruzicka, Jeger, and Redel, *Helv. Chim. Acta*, 1943, **26**, 1235.

The preparation [3] of ursa-9(11) : 12-dien-3-one from ursa-9(11) : 12-dien-3β-ol has been improved by replacing chromic–acetic acid by the chromic acid–pyridine complex [4] as oxidising agent, oxidation of the conjugated diene system being thereby lessened; [5] a purer product is then obtained.

Experimental.—Rotations were measured in $CHCl_3$ and ultraviolet absorption spectra in EtOH solutions. Grade II alumina was used for chromatography.

Ursa-9(11) : 12-dien-3-one (II). Chromium trioxide (2·0 g.) in pyridine (20 c.c.) was added to a solution of ursa-9(11) : 12-dien-3β-ol (2·0 g.) in pyridine (20 c.c.), and the mixture kept at room temperature for 18 hr. with occasional shaking. A solution of the product, isolated in the usual manner, in benzene was filtered through alumina, the filtrate evaporated, and the residue crystallised from chloroform–methanol to give ursa-9(11) : 12-dien-3-one (1·3 g.) as needles, m. p. 164—166°, $[\alpha]_D$ +411°, +414° (*c*, 1·7, 1·0), $\lambda_{max.}$ 2820 Å (ε 10,200) (Found : C, 85·1; H, 11·15. Calc. for $C_{30}H_{44}O$: C, 85·2; H, 11·0%). It gives a red brown colour with tetranitromethane. Jacobs and Fleck [3] give m. p. 133—134°, $[\alpha]_D$ +412° (in pyridine), and Spring and Vickerstaff [3] give m. p. 135—137° for this compound. The oxime crystallised from chloroform–methanol as needles, m. p. 249—250° (decomp.), $\lambda_{max.}$ 2060 and 2820 Å (ε 4700 and 9400) (Found : C, 82·6; H, 10·9. Calc. for $C_{30}H_{47}ON$: C, 82·3; H, 10·8%). Jacobs and Fleck [3] give m. p. 233—235° and Spring and Vickerstaff [3] give m. p. 236°.

Oleana-11 : 13(18)-dien-3-one (III). Chromium trioxide (280 mg.) in acetic acid (5 c.c.) was added to oleana-11 : 13(18)-dien-3β-ol (1·0 g.) in acetic acid (600 c.c.) at 30°, and the mixture kept at room temperature for 50 hr. *Oleana-11 : 13(18)-dien-3-one* isolated in the usual way and chromatographed on alumina, crystallised from chloroform–methanol as needles, m. p. 236—240°, $[\alpha]_D$ −48·5° (*c*, 0·8), $\lambda_{max.}$ 2420, 2500, and 2600 Å (ε 28,200, 32,400, and 21,100) (Found : C, 85·2; H, 10·8. $C_{30}H_{46}O$ requires C, 85·2; H, 11·0%). It gives a red-brown colour with tetranitromethane. The *oxime* crystallised from chloroform–methanol as needles, m. p. 279—280° (decomp.), $\lambda_{max.}$ 2420, 2510, and 2600 Å (ε 29,200, 32,000, and 20,700) (Found : C, 82·1; H, 10·9. $C_{30}H_{47}ON$ requires C, 82·3; H, 10·8%).

Conversion of ursa-9(11) : 12-dien-3-one (II) *into oleana-11 : 13(18)-dien-3-one* (III). Ursa-9(11) : 12-dien-3-one (360 mg.) was heated with concentrated hydrochloric acid (5 c.c.) in acetic acid (30 c.c.) at 100° for 60 hr., with addition of hydrochloric acid (5 c.c.) after 24 and 48 hr. Concentration of the solution yielded needles (340 mg.), a solution of which in benzene was filtered through alumina (5 g.). The filtrate was evaporated and the solid (280 mg.) dissolved in light petroleum (b. p. 60—80°) and filtered through alumina (5 g.). The eluate (240 mg.) was crystallised twice from chloroform–methanol, to give oleana-11 : 13(18)-dien-3-one (110 mg.) as needles, m. p. and mixed m. p. 236—238°, $[\alpha]_D$ −48° (*c*, 1·0), $\lambda_{max.}$ 2430, 2510, and 2600 Å (ε 25,400, 28,500, and 18,400).

We thank the Department of Scientific and Industrial Research for a Maintenance Award (to J. I. S.).

THE ROYAL TECHNICAL COLLEGE, GLASGOW. [*Received, June 30th*, 1955.]

[3] Jacobs and Fleck, *J. Biol. Chem.*, 1930, **88**, 137; Spring and Vickerstaff, *J.*, 1937, 249.
[4] Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 222.
[5] Cf. Beaton, Shaw, Spring, Stevenson, and Strachan, *J.*, 1955, 2606.

92. *The Effect of Dissolved Oxygen on the Diamagnetic Susceptibility of Organic Liquids.*

By C. M. FRENCH and D. HARRISON.

EGGLESTON, EVANS, and RICHARDS [1] pointed out that many of the values recorded in the literature for the magnetic susceptibilities of organic liquids may be in error by as much as 1·7% because of the presence of dissolved oxygen. In view of the bearing of this on the interpretation of the considerable amount of earlier magnetochemical data, the present authors have investigated the matter further.

The existence and approximate magnitude of the effect can be demonstrated in the

[1] Eggleston, Evans, and Richards, *J.*, 1954, 941.

following way, without the use of specially designed susceptibility tubes. The susceptibility of a liquid which has been in contact with air for some time is first measured by the normal Gouy method. Air is then removed by bubbling pure dry hydrogen through the liquid for 2 hr. Then the liquid is driven directly, under hydrogen pressure, into the susceptibility tube used for the first measurement. The tube is tightly stoppered and the magnetic measurement repeated. The difference in forces observed in this way for benzene corresponds to a change in molar susceptibility of 0·40 unit, quite close to the value (0·46) obtained by Eggleston *et al.* by their degassing technique. It was found that the hydrogen-saturated liquid could be left in the susceptibility tube for several hours without appreciable change in susceptibility due to replacement of hydrogen by air. The method might therefore be capable of development into an accurate method for measuring air-free liquids without the use of specially designed tubes. By the same method, we have observed changes in molar susceptibility of 0·40 for acetone, 0·59 for ethyl methyl ketone, and 0·77 for diethyl ketoxime, showing that the effect is not restricted to hydrocarbons. In all cases, when the hydrogen-saturated liquid was shaken with air for 5 min., the susceptibility returned to its original value.

For various reasons we do not believe that the matter is as serious as suggested by Eggleston *et al.* In the first place, the values quoted above are derived from differences in absolute susceptibilities ($X^* - X$) calculated by means of the equations :

$$F = \alpha(Xd - \kappa_{air}); \quad F^* = \alpha(X^*d - \kappa_{air}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where F and F^* are the forces in mg. on similar cylindrical specimens of air-saturated and air-free liquid, d the density of the liquid, κ_{air} the volume susceptibility of air, and α a constant determined by the cross-sectional area of the specimen and the magnetic field strengths at its upper and lower ends. (All susceptibility values are expressed in -10^{-6} c.g.s. units.) The necessity of determining α directly is usually avoided by measuring also the force ($F_b$mg.) on a similar specimen of benzene. Under normal conditions of working, this benzene will be practically air-saturated, if organic liquids do in fact absorb air as rapidly as indicated by the spectrophotometric measurements of Eggleston *et al.* The susceptibility χ (which is not in general the same as X, and may therefore be termed the relative susceptibility) is calculated by means of the equation :

$$\chi = (\chi_b - \kappa_{air}/d_b) \, . \, Fd_b/F_bd + \kappa_{air}/d \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where χ_b is an assumed value for the susceptibility of air-saturated benzene. For a similar determination with only air-free liquids, the susceptibility χ^* is calculated from the equation :

$$\chi^* = (\chi_b^* - \kappa_{air}/d_b) \, . \, F^*d_b/F_b^*d + \kappa_{air}/d \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

If for χ_b and χ_b^* the corresponding absolute susceptibilities X_b and X_b^* are used, the differences ($\chi^* - \chi$) and ($X^* - X$) are identical. In practice, a value of 0·702 is usually taken for the specific susceptibility of benzene, irrespective of the air content, *i.e.*, $\chi_b = \chi_b^* = 0{\cdot}702$. Under these conditions, it can easily be shown that $\chi^* - \chi < X^* - X$; thus from equation (1), the difference in absolute susceptibilities of air-saturated and air-free liquids is given by the equation

$$F - F^* = \alpha(Xd - X^*d) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$\therefore \; X - X^* = (F - F^*)/\alpha d \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Subtracting equation (3) from (2) we have :

$$\chi - \chi^* = \frac{1}{d}\left[\frac{F}{F_b}(\chi_b d_b - \kappa_{air}) - \frac{F^*}{F_b^*}(\chi_b^* d_b - \kappa_{air})\right] \quad . \quad . \quad . \quad . \quad (6)$$

But from (1),

$$F_b = \alpha\,(\chi_b d_b - \kappa_{air});\ F_b^* = \alpha(\chi_b^* d_b - \kappa_{air})$$

if the values taken for χ_b and χ_b^* are the absolute susceptibilities, X_b and X_b^*.

Then $$(\chi_b d_b - \kappa_{air})/F_b = (\chi_b^* d_b - \kappa_{air})/F_b^* = 1/\alpha$$

$\therefore$ from (6)

$$\chi - \chi^* = F/\alpha d - F^*/\alpha d$$
$$= X - X^*$$

In practice, the same value (0·702) is taken for χ_b irrespective of air content, *i.e.*, $\chi_b = \chi_b^* = 0{\cdot}702$. Since presumably this is the absolute susceptibility X_b of air-saturated benzene,

$$(\chi_b d_b - \kappa_{air}) = (\chi_b^* d_b - \kappa_{air})$$
$$= F_b/\alpha$$

Under these conditions, equation (6) becomes

$$\chi - \chi^* = \frac{F_b}{\alpha d}\left[\frac{F}{F_b} - \frac{F^*}{F_b^*}\right]$$
$$= X - X^* + \frac{F_b F^*}{\alpha d}\left(\frac{1}{F_b} - \frac{1}{F_b^*}\right)$$

Now α, F_b, and F_b^* are negative, and since we are dealing here with diamagnetic liquids F^* is also negative, and F_b^* is numerically greater thab F_b; the last term will thus be positive. Since χ^* is greater than χ, this can be rewritten :

$$\chi^* - \chi = X^* - X - \frac{F_b F^*}{\alpha d}\left(\frac{1}{F_b} - \frac{1}{F_b^*}\right)$$

i.e.,

$$(\chi^* - \chi) < (X^* - X)$$

For instance, in the case of acetone, $\chi^* - \chi$ is 0·0025, compared with a value of 0·0069 for $X^* - X$. This indicates that, with the normal method of measurement and calculation, the effect is much less serious than at first appeared likely. A similar reduction was shown for the other liquids studied. Looked at in another way, the effect of dissolved air in the liquid being measured is compensated, to some extent, by the presence of air in the standard liquid (benzene) used. In this discussion it is assumed that all measurements are made at the same temperature, otherwise the position is complicated by variation both in the amount of dissolved oxygen and in its paramagnetic susceptibility. It is likely that much of the earlier work on the variation of the susceptibility of diamagnetic liquids with temperature is invalidated by the presence of significant amounts of dissolved oxygen.

Much of the discussion in magnetochemical work on organic compounds is concerned with susceptibility increments between pairs of liquids. It would seem reasonable to suppose that in many cases both liquids will contain a certain amount of dissolved air; hence the error in the increment will be considerably less than that in either of the individual susceptibility values.

In conclusion, two points, not specifically considered by Eggleston *et al.*, must be mentioned. Since the magnetic force on a particular liquid specimen depends both on its specific susceptibility (χ) and its density (d), it is conceivable that the observed changes in F might be due to alteration in d, χ remaining constant. It is not easy to test this by direct experiment, but, in the case of benzene, our observed value of $F - F^*$ corresponds to a density difference of 0·006 on the assumption that $\chi = \chi^*$. It appears unlikely that simple replacement of one dissolved gas by another, or even complete removal of dissolved

gas, should cause a change in density of this magnitude. Nevertheless, the possibility that change in density might have a small effect on the observed value of $F - F^*$ cannot be entirely ruled out. A further point is that if the oxygen actually reacts with the liquid to give a trace of diamagnetic product, the effect on χ should be negligible. This is probably the case with aliphatic aldehydes (but not with ketones, as the present results show), and may explain, at least in part, the fact that these compounds have consistently higher susceptibilities (numerically)[2] than the isomeric ketones.

QUEEN MARY COLLEGE, MILE END ROAD, LONDON, E.1. [*Received, May 4th*, 1955.]

[2] Angus, Llewelyn, and Stott, *Trans. Faraday Soc.*, 1955, **51**, 241.

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93. *Studies in Aromatic Nucleophilic Substitution. Part V.* The Influence of the Solvent.*

By C. W. L. BEVAN and G. C. BYE.

IN the reactions of amines with halogenonitrobenzenes (cf. Chapman and Parker [1]) it is almost certainly true that the greater reactivity of activated aromatic fluoro- than of corresponding chloro-compounds is partly due to a high degree of solvation of the incipient fluoride ion.[2] This would be predicted on Hughes and Ingold's theory of solvent action,[3] but this theory would also predict a very much smaller solvent effect in reactions between a neutral molecule and an ion, so that differences in rate comparable to those found by Chapman and Parker [1] between replacement of fluoride and chloride ion from corresponding activated positions in an aromatic nucleus by ions such as the methoxide ion [4] are not explicable on this basis alone. However, it was of interest to see whether increasing the ionising power of the solvent did cause a large divergence of reactivity ratios, k_F/k_{Cl}. In halogenonitrobenzenes, k_F/k_{Cl} is $\sim 10^3$ and it is not possible to choose completely analogous compounds which react with methoxide ion in methanol at comparable rates. Thus, although reaction with *p*-fluoronitrobenzene is conveniently measured, that with *p*-chloronitrobenzene takes place only at such high temperatures that attack by alkali on the glass vessels would invalidate the results obtained in aqueous alcohol. The compounds chosen for comparison were *o*-fluoronitrobenzene and 1-chloro-2 : 4-dinitrobenzene and the ionising power of the solvent was increased by the addition up to 20% of water to methanol.[5] It was shown that in no case was the production of phenol (owing to the equilibrium $OMe^- + H{\cdot}OH \rightleftharpoons Me{\cdot}OH + OH^-$) greater than $5 \pm 1\frac{1}{2}\%$. This is in accord with Caldin and Long's results.[6]

The results obtained, together with certain data from the literature, are assembled in Table 1. They show that increasing the ionising power of the solvent by the addition of water causes a slight increase in the bimolecular rate constants. The rate for the fluoro-compound increases by 36%, and that of the chloro-compound by 14% on the addition of 20% by weight of water. This increase is contrary to expectation [7] and the difference between fluoride- and chloride-ion displacement produced by increasing the ionising power of the solvent does not seem sufficient for solvation effects to account for the large absolute difference in rate of displacement. The apparent discrepancy in Riklis's results (Table 1) may be due to (*a*) attack by alkali on the glass and (*b*) the fact that *o*-chloronitrobenzene is reduced in absolute alcoholic solution, particularly above 70°.

* Parts I—IV, *J.*, 1951, 2340; 1953, 655; 1954, 3091; 1956, 254.

[1] Chapman and Parker, *J.*, 1951, 3301.
[2] Cf. Musgrave, *Quart. Rev.*, 1954, **8**, 354.
[3] Hughes and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 608.
[4] Bevan, *J.*, 1951, 2340; Miller, Beckwith, and Leahy, *J.*, 1952, 3550.
[5] Cf. Hughes, Ingold, Cooper, Dhar, MacNulty, and Woolf, *J.*, 1948, 2043.
[6] Caldin and Long, *Nature*, 1953, **171**, 583.
[7] Cf. Bunnett and Zahler, *Chem. Rev.*, 1951, **49**, 273.

TABLE 1. *Effect of addition of water on the methoxylation of halogenonitrobenzene in methanol (k_2 in l. sec.$^{-1}$ mole^{-1}).*

Substituents	MeOH (% by wt.)			Substituents	MeOH (% by wt.)		
o-Fluoronitro	100	90	80	1-Chloro-2 : 4-dinitro	100	90	80
$k_2 \times 10^4$ (28·18°)	1·78 [d]	2·02	2·35	$k_2 \times 10^3$ (14·95°) ...	9·40	10·2	10·7
E (kcal.)	19·93 [d]	—	19·52	E (kcal.)	17·43 [a]	—	17·30
$\log_{10} B$	10·71 [d]	—	10·53	$\log_{10} B$	11·26 [a]	—	11·16
o-Dinitro [b]	100	90	80	*o*-Chloronitro [c]	100	90	80
$k_2 \times 10^5$ (25°)	7·0	7·7	8·2	$k_2 \times 10^3$ (80°)	4·45	4·17	3·57

[a] Miller *et al.*, *J.*, 1952, 3552; [b] Lobry de Bruyn and Steger, *Rec. Trav. chim.*, 1899, **18**, 41; [c] Riklis, *J. Gen. Chem.* (*U.S.S.R.*), 1947, **17**, 1511; [d] Bevan and Bye, *J.*, 1954, 3091.

TABLE 2. *k_2 (l. sec.$^{-1}$ mole^{-1}) for reaction of halides with* OMe^- *in aqueous methanol.*

o-Fluoronitrobenzene

	80% MeOH			90% MeOH
Temp.	28·18°	40·00°	51·49°	28·18°
k_2	$2·35 \times 10^{-4}$	$8·06 \times 10^{-4}$	$2·44 \times 10^{-3}$	$2·02 \times 10^{-4}$

1-Chloro-2 : 4-dinitrobenzene

	80% MeOH			90% MeOH	100% MeOH
Temp.	4·98°	14·95°	25·00°	14·95°	14·95°
k_2	$3·66 \times 10^{-3}$	$1·072 \times 10^{-2}$	$2·99 \times 10^{-2}$	$1·02 \times 10^{-2}$	$9·40 \times 10^{-3}$

TABLE 3. *Determination of rate constants, k_2 (l. sec.$^{-1}$ mole^{-1}).*

Reaction of 1-chloro-2 : 4-dinitrobenzene with sodium methoxide in 80% methanol +20% water. Initially, [Halide] ≈ 0·019M, [NaOMe] ≈ 0·034M. Temp. 14·95°.

(*a*) Concns. in ml. of 0·01527N-NaOEt per 5·00 ml. of sample.

t (min.)	0	20·0	23·0	26·0	29·2	32·1	35·0	38·0	41·0	45·1	49·1	51·0	∞
[NaOMe] ...	11·27	9·20	8·98	8·80	8·59	8·42	8·26	8·16	7·98	7·81	7·60	7·59	5·02
[Halide]	6·25	4·18	3·96	3·78	3·57	3·40	3·24	3·14	2·96	2·79	2·58	2·57	0·00
$10^2 k_2$	—	1·09	1·09	1·07	1·08	1·08	1·08	1·05	1·07	1·06	1·09	1·05	—

Mean $k_2 = 1·07 \times 10^{-2}$.

(*b*) Concns. in ml. of 0·01491N-$AgNO_3$ per 5·00 ml. of sample.

t (min.)	0	13·0	18·2	20·0	22·0	25·1	28·1	31·0	35·0	39·3	44·1	∞
[NaOMe] ...	11·46	10·0	9·56	9·41	9·27	9·03	8·86	8·68	8·46	8·26	8·03	5·17
[Halide]	6·29	4·83	4·39	4·24	4·10	3·86	3·69	3·51	3·29	3·09	2·86	0·00
$10^2 k_2$	—	1·07	1·07	1·07	1·07	1·08	1·07	1·07	1·07	1·06	1·07	—

Mean $k_2 = 1·07 \times 10^{-2}$.

Experimental.—Materials. *o*-Fluoronitrobenzene was prepared as by Bevan and Bye.[a]

1-Chloro-2 : 4-dinitrobenzene. An "AnalaR" specimen was crystallised from absolute ethanol to constant m. p. 51·0°.

Kinetic methods were as in previous papers of this series except that for the experiment in Table 3 (*b*) chloride ion was determined potentiometrically. Details of runs are given in Tables 2 and 3. The results in the latter Table establish the exact equivalence of the rate of loss of alkalinity and the rate of production of chloride ions.

In those methoxylations carried out in 80% methanol the yield of the corresponding phenol, which appeared to increase with temperature, was determined colorimetrically at the highest temperature used in studying the kinetics of these reactions. Standard solutions of the pure phenol, 1%, 2%, 3%, etc., were made up in a solvent of the composition used in rate measurements and containing an amount of sodium methoxide corresponding to its infinity concentration. "Infinity" tubes from runs were compared with these and in no case was the yield of phenol greated than 5%.

One of us (G. C. B.) thanks the Council of University College, Exeter, for a Scholarship, during the tenure of which this work was carried out.

UNIVERSITY COLLEGE, EXETER.
UNIVERSITY COLLEGE, IBADAN, NIGERIA.

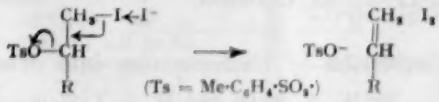
[*Received, June 27th, 1955.*]

[a] See ref. *d*, Table 1.

94. *The Action of Sodium Iodide on Methyl* 4 : 6-O-*Benzylidene*-3-*deoxy*-3-*iodo*-2-O-*toluene*-p-*sulphonyl*-α-D-*glucoside*.

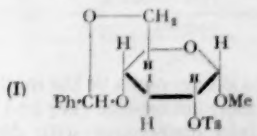
By F. H. Newth.

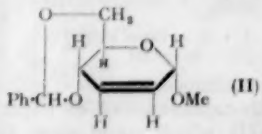
The reaction of di-toluene-*p*-sulphonates of terminal 1 : 2-glycols with sodium iodide in acetone leads to the formation of unsaturated products. Foster and Overend [1] suggest that the primary toluene-*p*-sulphonyloxy-group in ·CH(OTs)·CH_2·OTs first undergoes direct replacement by iodide and the resulting 1-deoxy-1-iodo-2-toluene-*p*-sulphonate is then attacked by iodide ion through the concerted mechanism :



rather than to give a vicinal di-iodide which then undergoes elimination of iodine as postulated by Bladon and Owen.[2] Foster and Overend's evidence is that 3 : 6-anhydro-1-deoxy-1-iodo-4 : 5-*O*-*iso*propylidene-2-*O*-toluene-*p*-sulphonyl-D-mannitol, although stable when heated alone in acetone, undergoes elimination with sodium iodide more readily than does 3 : 6-anhydro-4 : 5-*O*-*iso*propylidene-1 : 2-di-*O*-toluene-*p*-sulphonyl-D-mannitol, and that the reaction is effected also by anions other than iodide.

While there are no steric requirements in these acyclic compounds, in a cyclic compound it is self-evident that the iodine atom must be *trans* to the vicinal toluene-*p*-sulphonyloxy-group for ionic elimination to occur. Such a compound is methyl 4 : 6-*O*-benzylidene-3-deoxy-3-iodo-2-*O*-toluene-*p*-sulphonyl-α-D-glucoside (I).[3] This derivative has been treated with sodium iodide in acetone at 100° and after 10 min. sodium toluene-*p*-sulphonate, iodine, and methyl 4 : 6-*O*-benzylidene-2 : 3-didehydro-2 : 3-dideoxy-α-D-glucoside (II)[4, 5]





were formed quantitatively. The remarkable facility of this reaction provides support for Foster and Overend's formulation of elimination. Whether the yet unknown methyl 4 : 6-*O*-benzylidene-2 : 3-di-*O*-toluene-*p*-sulphonyl-α-D-mannoside could give an intermediate isomeric with (I) in the D-glucose or D-altrose series would depend upon the ability of iodide to replace either toluene-*p*-sulphonyloxy-group; it is significant that methyl 4 : 6-*O*-benzylidene-2 : 3-di-*O*-toluene-*p*-sulphonyl-α-D-glucoside is unaffected by sodium iodide in acetone.

The very easy elimination shown by (I) suggests that, in that compound, the iodide and the toluene-*p*-sulphonyloxy-group are to a substantial extent situated axially in the boat conformation of the pyranoside ring [6] (CI, IC interconversion is not possible because of the *trans* ring junction at $C_{(4)}$:$C_{(5)}$), a condition which would be favoured by electrostatic repulsion and steric interaction between the two groups.

Experimental.—Methyl 4 : 6-O-*benzylidene*-3-*deoxy*-3-*iodo*-2-O-*toluene*-p-*sulphonyl*-α-D-*glucoside*. This derivative, m. p. 136°, was obtained from methyl 4 : 6-*O*-benzylidene-3-deoxy-3-iodo-α-D-glucoside.[3]

Reaction of methyl 4 : 6-O-*benzylidene*-3-*deoxy*-3-*iodo*-2-O-*toluene*-p-*sulphonyl*-α-D-*glucoside with sodium iodide in acetone*. The derivative (100 mg.) was heated in acetone (5 ml.) containing

[1] Foster and Overend, *J.*, 1951, 3452.
[2] Bladon and Owen, *J.*, 1950, 598.
[3] Newth, Richards, and Wiggins, *J.*, 1950, 2356.
[4] Richards, *J.*, 1954, 4511.
[5] Bolliger and Prins, *Helv. Chim. Acta*, 1946, **29**, 1061.
[6] Newth, *J.*, 1956, 441.

sodium iodide (100 mg.) at 100°. Considerable reaction was apparent after 2 min. and heating was continued for 10 min. Sodium toluene-*p*-sulphonate weighed 34 mg. (96%), and iodine was equivalent to 3·55 ml. of 0·1N-thiosulphate (45 mg.; 98%). Acetone was evaporated and the aqueous portion was extracted with chloroform. This extract, when dried (Na_2SO_4) and evaporated, provided a crystalline residue (44 mg.) of methyl 4 : 6-*O*-benzylidene-2 : 3-dideoxy-α-D-glucoside, m. p. 117—119°. After recrystallising from ethanol it had m. p. 119—120°, $[\alpha]_D^{20}$ +129° (*c* 0·66 in $CHCl_3$). Richards [4] gives m. p. 119·5—120°, $[\alpha]_D^{28}$ +129°.

Methyl 4 : 6-*O*-benzylidene-2 : 3-di-*O*-toluene-*p*-sulphonyl-α-D-glucoside did not react with sodium iodide in acetone at 100° during 24 hr.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, August 15th*, 1955.]

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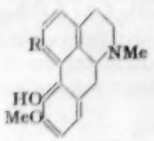
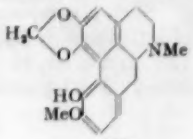
95. *The Conversion of Bulbocapnine into Morphothebaine.*

By W. A. AYER and W. I. TAYLOR.

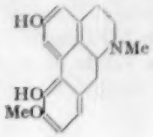
THE alkaloid *iso*thebaine is of interest since synthesis by any of the well-established routes leading to aporphines has not been possible and also because there is a difference of opinion as to whether its structure is really that given by the formula (I). Schlittler and Müller [1] degraded *O*-methyl*iso*thebaine to 3 : 4 : 5-trimethoxyphenanthrene which was synthesised by Pschorr and Koch's method.[2] However, Kiselev and Konovalova [3] obtained a trimethoxyphenanthrene picrate by the same degradative procedure but said that it depressed the melting point of 3 : 4 : 5-trimethoxyphenanthrene picrate prepared from morphenol.[4]



(I) : R = OMe
(II) : R = OH



(III)



(IV)

We have examined the fission with sodium and liquid ammonia of the methylenedioxy-group in bulbocapnine which we expected to afford morphothebaine (IV) and possibly the aporphine (II) which could then be converted into *iso*thebaine with diazomethane. However, the only phenolic product which could be isolated from the limited amount of bulbocapnine at our disposal was identical in all respects with morphothebaine prepared from thebaine.[5]

Experimental.—Bulbocapnine (400 mg.) was dissolved in ether (50 ml.) and liquid ammonia (500 ml.), and small pieces of sodium were added until the blue colour persisted for 1 hr. After the ammonia had been allowed to evaporate, the residue was taken up in water, and the alkaline solution extracted with chloroform which yielded unchanged bulbocapnine (130 mg.), m. p. 204° after one crystallization from ethanol. Excess of carbon dioxide was bubbled through the alkaline solution which was then extracted with chloroform to afford, after crystallization from ethanol, morphothebaine (165 mg.), m. p. and mixed m. p. 196—197° (Found : C, 72·4; H, 6·7; N, 4·8. Calc. for $C_{18}H_{19}O_3N$: C, 72·7; H, 6·5; N, 4·7%). The infrared spectrum was identical with a sample prepared from thebaine. Morphothebaine (30 mg.) was the only product which could be isolated from the crystallisation mother-liquors.

We thank Dr. E. Schlittler of Ciba Pharmaceutical Products Inc. for the bulbocapnine and thebaine, and the National Research Council of Canada for a grant and a N.R.C. Studentship (to W. A. A.).

UNIVERSITY OF NEW BRUNSWICK, FREDERICTON, CANADA. [*Received, September 15th*, 1955.]

[1] Schlittler and Müller, *Helv. Chim. Acta*, 1948, **31**, 1119.
[2] Pschorr and Koch, *Annalen*, 1912, **391**, 40.
[3] Kiselev and Konovala, *J. Gen. Chem.* (*U.S.S.R.*), 1949, **19**, 148.
[4] Vongerichten and Dittmer, *Ber.*, 1906, **39**, 1718.
[5] Howard, *Ber.*, 1884, **17**, 527.

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M. Peligot has communicated to the Annales de Chimie et Physique (xvii, 368) a short note on the preparation of uranium. A mixture of 75 grammes of uranous chloride, 150 grammes of dry potassium chloride, and 50 grammes of sodium in fragments is introduced into a porcelain crucible, itself surrounded by a plumbago crucible. The reaction is effected in a wind furnace at the temperature of redness; but the heat must be increased for a short time at the close of the operation. In the black slag may be found, after cooling, globules of fused uranium.

M. Peligot finds uranium

The new method of producing uranium was announced in the first issue of Nature in 1869. Monsieur Peligot, who twenty-eight years before had first isolated the metal, discovered by Klaproth in 1789, was opening the door a little more widely to the possibility of an Atomic Age a century later. In recent years the priority attaching to the atomic energy programme has restricted their availability, but uranium compounds are now again available and figure among the several thousand fine chemicals of very high purity supplied by B.D.H. for science and industry. The B.D.H. catalogue contains more than 6,000 laboratory chemicals and reagents. Of these some hundreds in addition to 'AnalaR' and 'M.A.R.' chemicals, are labelled with specifications of purity.

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